

P1 1174525

REC'D 28 MAY 2004

WIPO

PCT

# THE UNITED STATES OF AMERICA

**TO ALL TO WHOM THESE PRESENTS SHALL COME:**

**UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office**

**May 25, 2004**

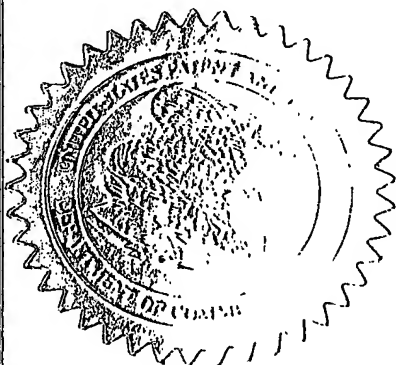
**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM  
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK  
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT  
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A  
FILING DATE.**

**APPLICATION NUMBER: 60/456,835**

**FILING DATE: March 21, 2003**

**RELATED PCT APPLICATION NUMBER: PCT/US04/08700**

**By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS**



*M. Sias*  
**M. SIAS  
Certifying Officer**

**PRIORITY  
DOCUMENT**

**SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)**

03/21/03  
JCS85 U.S. PTO

03-24-05456835-032119A/Rlo  
#

Attorney's Docket No. 046562/260517  
Express Mail Label No. EV 185284498 US

PATENT

JCS971 U.S. PTO  
60/456835

**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

Box Provisional Patent Application  
Commissioner for Patents  
Washington, DC 20231

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. 1.53(c).

INVENTOR(s)

Name: Matthew Oliver Fraser  
Residence: 408 Gablefield Lane  
Apex, NC 27502

Name: Karl Bruce Thor  
Residence: 109 Draymore Way  
Morrisville, NC 27560

Name: Edward C. Burgard  
Residence: 215 Cates Farm Road  
Chapel Hill, NC 27516

Name: Lee R. Brettman  
Residence: 183 Greystone Lane  
Sudbury, MA 01776

Name: Steven B. Landau  
Residence: 44 Tanglewood Road  
Wellesley, MA 02481

TITLE OF THE INVENTION (500 characters maximum)

METHODS FOR TREATING LOWER URINARY TRACT DISORDERS USING  $\alpha_2\delta$   
SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE  
MODULATORS

CORRESPONDENCE ADDRESS

Edward R. Ergenzinger Jr.  
Registration No. 47,549  
Customer Number 00826

Tel Raleigh Office (919) 862-2200  
Fax Raleigh Office (919) 862-2260

Attorney Docket No. 046562/260517  
Filed: Concurrently Herewith  
Page 2

ENCLOSED APPLICATION PARTS (check all that apply)

- ☒ Specification (Number of Pages 86)  
☒ Drawing(s) (Number of Sheets 1 at page 61 of the specification)  
☐ Application Data Sheet. See 37 CFR 1.76  
☐ CD(s), Number  
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES

- ☐ Applicant claims small entity status  
☒ Check or money order is enclosed to cover the filing fee.  
☐ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 16-0605.  
☒ Please charge Deposit Account No. 16-0605 for any fee deficiency.

PROVISIONAL FILING FEE AMOUNT(s)

Large Entity \$160.00  
Small Entity \$ 80.00

Filing Fee Amount: \$80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ☒ No.  
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

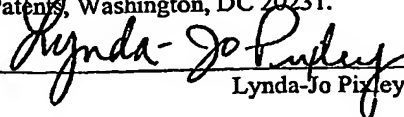


Edward R. Ergenzinger Jr.  
Registration No. 47,549  
Date: March 21, 2003

CUSTOMER NO. 00826  
ALSTON & BIRD LLP  
Bank of America Plaza  
101 South Tryon Street, Suite 4000  
Charlotte, NC 28280-4000  
Tel Raleigh Office (919) 862-2200  
Fax Raleigh Office (919) 862-2260

"Express Mail" mailing label number EV 185284498 US  
Date of Deposit March 21, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner For Patents, Washington, DC 20231.

  
Lynda-Jo Pixley

Attorney Docket No: 046562/260517

METHODS FOR TREATING LOWER URINARY TRACT DISORDERS USING  $\alpha_2\delta$   
SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE  
MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/435,021, filed December 20, 2002, which is hereby incorporated herein in its entirety by reference.

FIELD OF THE INVENTION

The invention relates to methods of using  $\alpha_2\delta$  subunit calcium channel modulators in combination with smooth muscle modulators for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients.

BACKGROUND OF THE INVENTION

Lower urinary tract disorders affect the quality of life of millions of men and women in the United States every year. Disorders of the lower urinary tract include overactive bladder, prostatitis and prostatic dysuria, interstitial cystitis, benign prostatic hyperplasia, and, in spinal cord injured patients, spastic bladder.

Overactive bladder is a treatable medical condition that is estimated to affect 17 to 20 million people in the United States. Current treatments for overactive bladder include medication, diet modification, programs in bladder training, electrical stimulation, and surgery. Currently, antimuscarinics (which are subtypes of the general class of anticholinergics) are the primary medication used for the treatment of overactive bladder. This treatment suffers from limited efficacy and side effects such as dry mouth, dry eyes, dry vagina, palpitations, drowsiness, and constipation, which have proven difficult for some individuals to tolerate.

Prostatitis and prostatic dysuria are other lower urinary tract disorders that have been suggested to affect approximately 2-9% of the adult male population (Collins M M, *et al.*, (1998) *J. Urology*, 159: 1224-1228). Currently, there are no established treatments for



prostatitis and prostatic dysuria. Antibiotics are often prescribed, but with little evidence of efficacy. COX-2 selective inhibitors and  $\alpha$ -adrenergic blockers have been suggested as treatments, but their efficacy has not been established. Hot sitz baths and anticholinergic drugs have also been employed to provide some symptomatic relief.

Interstitial cystitis is another lower urinary tract disorder of unknown etiology that predominantly affects young and middle-aged females, although men and children can also be affected. Past treatments for interstitial cystitis have included the administration of antihistamines, sodium pentosanpolysulfate, dimethylsulfoxide, steroids, tricyclic antidepressants and narcotic antagonists, although these methods have generally been unsuccessful (Sant, G. R. (1989) Interstitial cystitis: pathophysiology, clinical evaluation and treatment. *Urology Annals* 3: 171-196).

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that is very common in men over 40 years of age. Invasive treatments for BPH include transurethral resection of the prostate, transurethral incision of the prostate, balloon dilation of the prostate, prostatic stents, microwave therapy, laser prostatectomy, transrectal high-intensity focused ultrasound therapy and transurethral needle ablation of the prostate. However, complications may arise through the use of some of these treatments, including retrograde ejaculation, impotence, postoperative urinary tract infection and some urinary incontinence. Non-invasive treatments for BPH include androgen deprivation therapy and the use of 5 $\alpha$ -reductase inhibitors and  $\alpha$ -adrenergic blockers. However, these treatments have proven only minimally to moderately effective for some patients.

Lower urinary tract disorders are particularly problematic for individuals suffering from spinal cord injury. Following spinal cord injury, the bladder is usually affected in one of two ways: 1) "spastic" or "reflex" bladder, in which the bladder fills with urine and a reflex automatically triggers the bladder to empty; or 2) "flaccid" or "non-reflex" bladder, in which the reflexes of the bladder muscles are absent or slowed. Treatment options for these disorders usually include intermittent catheterization, indwelling catheterization, or condom catheterization, but these methods are invasive and frequently inconvenient. Urinary sphincter muscles may also be affected by spinal cord injuries, resulting in an inability of urinary sphincter muscles to relax when the bladder

contracts ("dyssynergia"). Traditional treatments for dyssynergia include medications that have been somewhat inconsistent in their efficacy or surgery.

Because existing therapies and treatments for lower urinary tract disorders in normal and spinal cord injured patients are associated with limitations as described above, new therapies and treatments are therefore desirable.

### SUMMARY OF THE INVENTION

Compositions and methods for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients, are provided. Compositions of the invention comprise  $\alpha_2\delta$  subunit calcium channel modulators or other compounds that bind to the  $\alpha_2\delta$  calcium channel subunit in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. Compositions of the invention include combinations of the aforementioned compounds as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof.

The compositions are administered in therapeutically effective amounts to a patient in need thereof for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. It is recognized that the compositions may be administered by any means of administration as long as an effective amount for the treatment of painful and non-painful symptoms associated with lower urinary tract disorders in normal and spinal cord injured patients is delivered. The compositions may be formulated, for example, for sustained, continuous, or as-needed administration.

### DETAILED DESCRIPTION OF THE INVENTION

#### Overview and Definitions

The present invention provides compositions and methods for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. The lower urinary tract disorders of the present invention include, but are not limited to such disorders as painful and non-painful overactive bladder, prostatitis and prostatic dysplasia, interstitial cystitis, benign prostatic hyperplasia, and, in spinal cord injured patients, and

spastic bladder. The compositions comprise a therapeutically effective dose of an  $\alpha_2\delta$  subunit calcium channel modulator, including gabapentin and pregabalin, in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. The methods are accomplished by administering, for example, various compositions and formulations that contain quantities of an  $\alpha_2\delta$  subunit calcium channel modulator and/or other compounds that bind to  $\alpha_2\delta$  subunit-containing calcium channels in combination with one or more compounds with smooth muscle modulatory effects.

The present inventions now will be described more fully hereinafter with reference to the accompanying drawings, in which some, but not all embodiments of the invention are shown. Indeed, these inventions may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Like numbers refer to like elements throughout.

Many modifications and other embodiments of the inventions set forth herein will come to mind to one skilled in the art to which these inventions pertain having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the inventions are not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

It must be noted that as used in this specification and the appended embodiments, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well as two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

By "non-painful" is intended sensations or symptoms including mild or general discomfort that a patient subjectively describes as not producing or resulting in pain.

By "painful" is intended sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

By "lower urinary tract" is intended all parts of the urinary system except the kidneys. By "lower urinary tract disorder" is intended any disorder involving the lower urinary tract, including but not limited to overactive bladder, prostatitis, interstitial cystitis, benign prostatic hyperplasia, and spastic and flaccid bladder. By "non-painful lower urinary tract disorder" is intended any lower urinary tract disorder involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. By "painful lower urinary tract disorder" is intended any lower urinary tract disorder involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

By "bladder disorder" is intended any condition involving the urinary bladder. By "non-painful bladder disorder" is intended any bladder disorder involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. By "painful bladder disorder" is intended any bladder disorder involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

By "overactive bladder" is intended any form of incontinence characterized by increased frequency of micturition or the desire to void, whether complete or episodic, and where loss of voluntary control ranges from partial to total and whether there is loss of urine (incontinence) or not. By "painful overactive bladder" is intended any form of overactive bladder, as defined above, involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain. By "non-painful overactive bladder" is intended any form of overactive bladder, as defined above, involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. Non-painful symptoms can include, but are not limited to, urinary urgency, incontinence, urge incontinence, stress incontinence, urinary frequency, and nocturia.

By "urinary urgency" is intended sudden strong urges to urinate with little or no chance to postpone the urination. By "incontinence" is meant the inability to control excretory functions, including urination (urinary incontinence). By "urge incontinence"

or "urinary urge incontinence" is intended the involuntary loss of urine associated with an abrupt and strong desire to void. By "stress incontinence" or "urinary stress incontinence" is intended a medical condition in which urine leaks when a person coughs, sneezes, laughs, exercises, lifts heavy objects, or does anything that puts pressure on the bladder. By "urinary frequency" is intended urinating more frequently than the patient desires. As there is considerable interpersonal variation in the number of times in a day that an individual would normally expect to urinate, "more frequently than the patient desires" is further defined as a greater number of times per day than that patient's historical baseline. "Historical baseline" is further defined as the median number of times the patient urinated per day during a normal or desirable time period. By "nocturia" is intended being awakened from sleep to urinate more frequently than the patient desires.

By "neurogenic bladder" or "neurogenic overactive bladder" is intended overactive bladder as described further herein that occurs as the result of neurological damage due to disorders including but not limited to stroke, Parkinson's disease, diabetes, multiple sclerosis, peripheral neuropathy, or spinal cord lesions.

By "detrusor hyperreflexia" is intended a condition characterized by uninhibited detrusor, wherein the patient has some sort of neurologic impairment. By "detrusor instability" or "unstable detrusor" is intended conditions where there is no neurologic abnormality.

By "prostatitis" is intended any type of disorder associated with an inflammation of the prostate, including chronic bacterial prostatitis and chronic non-bacterial prostatitis. By "non-painful prostatitis" is intended prostatitis involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. By "painful prostatitis" is intended prostatitis involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

"Chronic bacterial prostatitis" is used in its conventional sense to refer to a disorder associated with symptoms that include inflammation of the prostate and positive bacterial cultures of urine and prostatic secretions. "Chronic non-bacterial prostatitis" is used in its conventional sense to refer to a disorder associated with symptoms that include

inflammation of the prostate and negative bacterial cultures of urine and prostatic secretions. "Prostodynia" is used in its conventional sense to refer to a disorder generally associated with painful symptoms of chronic non-bacterial prostatitis as defined above, without inflammation of the prostate. "Interstitial cystitis" is used in its conventional sense to refer to a disorder associated with symptoms that include irritative voiding symptoms, urinary frequency, urgency, nocturia, and suprapubic or pelvic pain related to and relieved by voiding.

"Benign prostatic hyperplasia" is used in its conventional sense to refer to a disorder associated with benign enlargement of the prostate gland.

"Spastic bladder" or "reflex bladder" is used in its conventional sense to refer to a condition following spinal cord injury in which bladder emptying has become unpredictable.

"Flaccid bladder" or "non-reflex bladder" is used in its conventional sense to refer to a condition following spinal cord injury in which the reflexes of the bladder muscles are absent or slowed.

"Dyssynergia" is used in its conventional sense to refer to a condition following spinal cord injury in which patients characterized by an inability of urinary sphincter muscles to relax when the bladder contracts.

"Vulvodynia" is used in its conventional sense to refer to a condition characterized by gynecologic syndrome characterized by unexplained vulvar pain, sexual dysfunction, and psychological disability.

"Vulvar vestibulitis" (also known as "vulvar vestibulitis syndrome," "focal vulvitis," and "vestibular adenitis") is used in its conventional sense to refer to a condition that is a subtype of vulvodynia characterized by: 1) pain on vestibular touch or attempted vaginal entry; 2) tenderness to Q-tip pressure localized within the vulvar vestibule; 3) physical findings confined to vestibular erythema of various degrees; and 4) an exclusion of other causes for vestibular erythema and tenderness, such as candidiasis (yeast infections) or herpes infections. Other symptoms may include itching, swelling and excoriation.

The terms "active agent" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical compound that induces a desired effect, i.e.,

in this case, treatment of painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. The primary active agents herein are  $\alpha_2\delta$  subunit calcium channel modulators and/or smooth muscle relaxants. The present invention comprises a combination therapy wherein an  $\alpha_2\delta$  subunit calcium channel modulator is administered with one or more smooth muscle modulator. Such combination therapy may be carried out by administration of the different active agents in a single composition, by concurrent administration of the different active agents in different compositions, or by sequential administration of the different active agents. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned that also induce the desired effect.

The term " $\alpha_2\delta$  subunit calcium channel modulator" as used herein refers to an agent that is capable of binding to the  $\alpha_2\delta$  subunit of a calcium channel, including subtypes of the  $\alpha_2\delta$  calcium channel subunit as disclosed in Klugbauer et al. (1999) *J. Neurosci.* 19: 684-691, to produce a physiological effect, such as opening, closing, or blocking the channel. Unless otherwise indicated, the term " $\alpha_2\delta$  subunit calcium channel modulator" is intended to include gabapentin, pregabalin, and compounds that bind to the  $\alpha_2\delta$  calcium channel subunit as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "smooth muscle modulator" as used herein refers to any compound that inhibits or blocks the contraction of smooth muscles, including but not limited to antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. Smooth muscle modulators can be "direct" (also known as "musculotropic") or "indirect" (also known as "neurotropic"). "Direct smooth muscle modulators" are smooth muscle modulators that act by inhibiting or blocking contractile mechanisms within smooth muscle, including but not limited to modification of the interaction between actin and myosin. "Indirect smooth muscle modulators" are smooth muscle modulators that act by inhibiting or blocking neurotransmission that results in the contraction of smooth muscle, including but not

limited to blockade of presynaptic facilitation of acetylcholine release at the axon terminal of motor neurons terminating in smooth muscle.

The term "anticholinergic agent" as used herein refers to any acetylcholine receptor antagonist, including antagonists of nicotinic and/or muscarinic acetylcholine receptors. The term "antinicotinic agent" as used herein is intended any nicotinic acetylcholine receptor antagonist. The term "antimuscarinic agent" as used herein is intended any muscarinic acetylcholine receptor antagonist. Unless otherwise indicated, the terms "anticholinergic agent," "antinicotinic agent," and "antimuscarinic agent" are intended to include anticholinergic, antinicotinic, and antimuscarinic agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term " $\beta$ 3 adrenergic agonist" is used in its conventional sense to refer to a compound that binds to and agonizes  $\beta$ 3 adrenergic receptors. Unless otherwise indicated, the term " $\beta$ 3 adrenergic agonist" is intended to include  $\beta$ 3 adrenergic agonist agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "spasmolytic" (also known as "antispasmodic") is used in its conventional sense to refer to a compound that relieves or prevents muscle spasms, especially of smooth muscle. Unless otherwise indicated, the term "spasmolytic" is intended to include spasmolytic agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "neurokinin receptor antagonist" is used in its conventional sense to refer to a compound that binds to and antagonizes neurokinin receptors. Unless otherwise indicated, the term "neurokinin receptor antagonist" is intended to include neurokinin receptor antagonist agents as disclosed further herein, as well as salts, esters,



amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "bradykinin receptor antagonist" is used in its conventional sense to refer to a compound that binds to and antagonizes bradykinin receptors. Unless otherwise indicated, the term "bradykinin receptor antagonist" is intended to include bradykinin receptor antagonist agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "nitric oxide donor" is used in its conventional sense to refer to a compound that releases free nitric oxide when administered to a patient. Unless otherwise indicated, the term "nitric oxide donor" is intended to include nitric oxide donor agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The terms "treating" and "treatment" as used herein refer to relieving the painful or non-painful symptoms or other clinically observed sequelae for clinically diagnosed disorders as described herein, including disorders associated with lower urinary tract in normal and spinal cord injured patients.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., relieving the painful and non-painful symptoms associated with lower urinary tract disorders in normal and spinal cord injured patients, as explained above. It is recognized that the effective amount of a drug or pharmacologically active agent will vary depending on the route of administration, the selected compound, and the species to which the drug or pharmacologically active agent is administered. It is also recognized that one of skill in the art will determine appropriate effective amounts by taking into account such factors as metabolism, bioavailability, and other factors that affect plasma levels of a drug or pharmacologically

active agent following administration within the unit dose ranges disclosed further herein for different routes of administration.

By "pharmaceutically acceptable," such as in the recitation of a "pharmaceutically acceptable carrier," or a "pharmaceutically acceptable acid addition salt," is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" derivative or metabolite, refers to a derivative or metabolite having the same type of pharmacological activity as the parent compound. When the term "pharmaceutically acceptable" is used to refer to a derivative (e.g., a salt or an analog) of an active agent, it is to be understood that the compound is pharmacologically active as well, i.e., therapeutically effective for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients.

By "continuous" dosing is meant the chronic administration of a selected active agent. By "as-needed" dosing, also known as "*pro re nata*" "prn" dosing, and "on demand" dosing or administration is meant the administration of a single dose of the active agent at some time prior to commencement of an activity wherein suppression of the painful and non-painful symptoms of a lower urinary tract disorder in normal and spinal cord injured patients, would be desirable. Administration can be immediately prior to such an activity, including about 0 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, or about 10 hours prior to such an activity, depending on the formulation.

By "short-term" is intended any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes after drug administration.

By "rapid-offset" is intended any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2

hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes after drug administration.

The term "controlled release" is intended to refer to any drug-containing formulation in which release of the drug is not immediate, i.e., with a "controlled release" formulation, oral administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "non-immediate release" as defined in Remington: The Science and Practice of Pharmacy, Twentieth Ed. (Philadelphia, Pa.: Lippincott Williams & Wilkins, 2000).

The "absorption pool" represents a solution of the drug administered at a particular absorption site, and  $k_r$ ,  $k_a$ , and  $k_e$  are first-order rate constants for: 1) release of the drug from the formulation; 2) absorption; and 3) elimination, respectively. For immediate release dosage forms, the rate constant for drug release  $k_r$  is far greater than the absorption rate constant  $k_a$ . For controlled release formulations, the opposite is true, i.e.,  $k_r \ll k_a$ , such that the rate of release of drug from the dosage form is the rate-limiting step in the delivery of the drug to the target area. The term "controlled release" as used herein includes any nonimmediate release formulation, including but not limited to sustained release, delayed release and pulsatile release formulations.

The term "sustained release" is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period such as up to about 72 hours, about 66 hours, about 60 hours, about 54 hours, about 48 hours, about 42 hours, about 36 hours, about 30 hours, about 24 hours, about 18 hours, about 12 hours, about 10 hours, about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour after drug administration.

The term "delayed release" is used in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that preferably, although not necessarily, includes a delay of up to about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours.

The term "pulsatile release" is used in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration. The term "immediate release" is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

By the term "transdermal" drug delivery is meant delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream.

The term "topical administration" is used in its conventional sense to mean delivery of a topical drug or pharmacologically active agent to the skin or mucosa.

The term "oral administration" is used in its conventional sense to mean delivery of a drug through the mouth and ingestion through the stomach and digestive tract.

The term "inhalation administration" is used in its conventional sense to mean delivery of an aerosolized form of the drug by passage through the nose or mouth during inhalation and passage of the drug through the walls of the lungs.

The term "intravesical administration" is used in its conventional sense to mean delivery of a drug directly into the bladder.

By the term "parenteral" drug delivery is meant delivery by passage of a drug into the blood stream without first having to pass through the alimentary canal, or digestive tract. Parenteral drug delivery may be "subcutaneous," referring to delivery of a drug by administration under the skin. Another form of parenteral drug delivery is "intramuscular," referring to delivery of a drug by administration into muscle tissue. Another form of parenteral drug delivery is "intradermal," referring to delivery of a drug by administration into the skin. An additional form of parenteral drug delivery is "intravenous," referring to delivery of a drug by administration into a vein. An additional form of parenteral drug delivery is "intra-arterial," referring to delivery of a drug by administration into an artery. Another form of parenteral drug delivery is "transdermal," referring to delivery of a drug by passage of the drug through the skin and into the bloodstream. Another form of parenteral drug delivery is "intrathecal," referring to delivery of a drug directly into the intrathecal space (where fluid flows around the spinal cord).

Still another form of parenteral drug delivery is "transmucosal," referring to administration of a drug to the mucosal surface of an individual so that the drug passes through the mucosal tissue and into the individual's blood stream. Transmucosal drug delivery may be "buccal" or "transbuccal," referring to delivery of a drug by passage through an individual's buccal mucosa and into the bloodstream. Another form of transmucosal drug delivery herein is "lingual" drug delivery, which refers to delivery of a drug by passage of a drug through an individual's lingual mucosa and into the bloodstream. Another form of transmucosal drug delivery herein is "sublingual" drug delivery, which refers to delivery of a drug by passage of a drug through an individual's sublingual mucosa and into the bloodstream. Another form of transmucosal drug delivery is "nasal" or "intranasal" drug delivery, referring to delivery of a drug through an individual's nasal mucosa and into the bloodstream. An additional form of transmucosal drug delivery herein is "rectal" or "transrectal" drug delivery, referring to delivery of a drug by passage of a drug through an individual's rectal mucosa and into the bloodstream. Another form of transmucosal drug delivery is "urethral" or "transurethral" delivery, referring to delivery of the drug into the urethra such that the drug contacts and passes through the wall of the urethra. An additional form of transmucosal drug delivery is "vaginal" or "transvaginal" delivery, referring to delivery of a drug by passage of a drug through an individual's vaginal mucosa and into the bloodstream. An additional form of transmucosal drug delivery is "perivaginal" delivery, referring to delivery of a drug through the vaginolabial tissue into the bloodstream.

In order to carry out the method of the invention, a selected active agent is administered to a patient suffering from a painful or non-painful lower urinary tract disorder in normal and spinal cord injured patients. A therapeutically effective amount of the active agent may be administered orally, intravenously, subcutaneously, transmucosally (including buccally, sublingually, transurethrally, and rectally), topically, transdermally, by inhalation, intravesically, intrathecally or using any other route of administration.

#### Lower Urinary Tract Disorders

Lower urinary tract disorders affect the quality of life of millions of men and

women in the United States every year. While the kidneys filter blood and produce urine, the lower urinary tract is concerned with storage and elimination of this waste liquid and includes all other parts of the urinary tract except the kidneys. Generally, the lower urinary tract includes the ureters, the urinary bladder, and the urethra. Disorders of the lower urinary tract include painful and non-painful overactive bladder, prostatitis and prostatic dysplasia, interstitial cystitis, benign prostatic hyperplasia, and, in spinal cord injured patients, spastic bladder and flaccid bladder.

Overactive bladder is a treatable medical condition that is estimated to affect 17 to 20 million people in the United States. Symptoms of overactive bladder include urinary frequency, urgency, nocturia (the disturbance of nighttime sleep because of the need to urinate) and urge incontinence (accidental loss of urine) due to a sudden and unstoppable need to urinate. As opposed to stress incontinence, in which loss of urine is associated with physical actions such as coughing, sneezing, exercising, or the like, urge incontinence is usually associated with an overactive detrusor muscle (the smooth muscle of the bladder which contracts and causes it to empty).

There is no single etiology for overactive bladder. Neurogenic overactive bladder (or neurogenic bladder) occurs as the result of neurological damage due to disorders such as stroke, Parkinson's disease, diabetes, multiple sclerosis, peripheral neuropathy, or spinal cord lesions. In these cases, the overactivity of the detrusor muscle is termed detrusor hyperreflexia. By contrast, non-neurogenic overactive bladder can result from non-neurological abnormalities including bladder stones, muscle disease, urinary tract infection or drug side effects.

Due to the enormous complexity of micturition (the act of urination) the exact mechanism causing overactive bladder is unknown. Overactive bladder may result from hypersensitivity of sensory neurons of the urinary bladder, arising from various factors including inflammatory conditions, hormonal imbalances, and prostate hypertrophy. Destruction of the sensory nerve fibers, either from a crushing injury to the sacral region of the spinal cord, or from a disease that causes damage to the dorsal root fibers as they enter the spinal cord may also lead to overactive bladder. In addition, damage to the spinal cord or brain stem causing interruption of transmitted signals may lead to

abnormalities in micturition. Therefore, both peripheral and central mechanisms may be involved in mediating the altered activity in overactive bladder.

In spite of the uncertainty regarding whether central or peripheral mechanisms, or both, are involved in overactive bladder, many proposed mechanisms implicate neurons and pathways that mediate non-painful visceral sensation. Pain is the perception of an aversive or unpleasant sensation and may arise through a variety of proposed mechanisms. These mechanisms include activation of specialized sensory receptors that provide information about tissue damage (nociceptive pain), or through nerve damage from diseases such as diabetes, trauma or toxic doses of drugs (neuropathic pain) (See, e.g., A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.; Benevento *et al.* (2002) *Physical Therapy Journal* 82:601-12). Nociception may give rise to pain, but not all stimuli that activate nociceptors are experienced as pain (A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.). Somatosensory information from the bladder is relayed by nociceptive A $\delta$  and C fibers that enter the spinal cord via the dorsal root ganglion (DRG) and project to the brainstem and thalamus via second or third order neurons (Andersson (2002) *Urology* 59:18-24; Andersson (2002) *Urology* 59:43-50; Morrison, J., Steers, W.D., Brading, A., Blok, B., Fry, C., de Groat, W.C., Kakizaki, H., Levin, R., and Thor, K.B., "Basic Urological Sciences" In: Incontinence (vol. 2) Abrams, P. Khoury, S., and Wein, A. (Eds.) Health Publications, Ltd., Plymbridge Distributors, Ltd., Plymouth, UK., (2002). A number of different subtypes of sensory afferent neurons may be involved in neurotransmission from the lower urinary tract. These may be classified as, but not limited to, small diameter, medium diameter, large diameter, myelinated, unmyelinated, sacral, lumbar, peptidergic, non-peptidergic, IB4 positive, IB4 negative, C fiber, A $\delta$  fiber, high threshold or low threshold neurons. Nociceptive input to the DRG is thought to be conveyed to the brain along several ascending pathways, including the spinothalamic, spinoreticular, spinomesencephalic, spinocervical, and in some cases dorsal column/medial lemniscal tracts (A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.). Central mechanisms, which are not fully understood, are thought to convert some, but not

all, nociceptive information into painful sensory perception (A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.).

Current treatments for overactive bladder include medication, diet modification, programs in bladder training, electrical stimulation, and surgery. Currently, antimuscarinics (which are subtypes of the general class of anticholinergics) are the primary medication used for the treatment of overactive bladder. This treatment suffers from limited efficacy and side effects such as dry mouth, dry eyes, dry vagina, palpitations, drowsiness, and constipation, which have proven difficult for some individuals to tolerate.

Prostatitis and prostatic pain are other lower urinary tract disorders that have been suggested to affect approximately 2-9% of the adult male population (Collins M M, et al., (1998) "How common is prostatitis? A national survey of physician visits," *Journal of Urology*, 159: 1224-1228). Prostatitis is associated with an inflammation of the prostate, and may be subdivided into chronic bacterial prostatitis and chronic non-bacterial prostatitis. Chronic bacterial prostatitis is thought to arise from bacterial infection and is generally associated with such symptoms as inflammation of the prostate, the presence of white blood cells in prostatic fluid, and/or pain. Chronic non-bacterial prostatitis is an inflammatory and painful condition of unknown etiology characterized by excessive inflammatory cells in prostatic secretions despite a lack of documented urinary tract infections, and negative bacterial cultures of urine and prostatic secretions. Prostatic pain (chronic pelvic pain syndrome) is a condition associated with the painful symptoms of chronic non-bacterial prostatitis without an inflammation of the prostate.

Currently, there are no established treatments for prostatitis and prostatic pain. Antibiotics are often prescribed, but with little evidence of efficacy. COX-2 selective inhibitors and  $\alpha$ -adrenergic blockers have been suggested as treatments, but their efficacy has not been established. Hot sitz baths and anticholinergic drugs have also been employed to provide some symptomatic relief.

Interstitial cystitis is another lower urinary tract disorder of unknown etiology that predominantly affects young and middle-aged females, although men and children can also be affected. Symptoms of interstitial cystitis may include irritative voiding symptoms, urinary frequency, urgency, nocturia and suprapubic or pelvic pain related to



and relieved by voiding. Many interstitial cystitis patients also experience headaches as well as gastrointestinal and skin problems. In some extreme cases, interstitial cystitis may also be associated with ulcers or scars of the bladder.

Past treatments for interstitial cystitis have included the administration of antihistamines, sodium pentosanpolysulfate, dimethylsulfoxide, steroids, tricyclic antidepressants and narcotic antagonists, although these methods have generally been unsuccessful (Sant, G. R. (1989) Interstitial cystitis: pathophysiology, clinical evaluation and treatment. *Urology Annal* 3: 171-196).

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that is very common in men over 40 years of age. BPH is thought to be due to excessive cellular growth of both glandular and stromal elements of the prostate. Symptoms of BPH include urinary frequency, urge incontinence, nocturia, and reduced urinary force and speed of flow.

Invasive treatments for BPH include transurethral resection of the prostate, transurethral incision of the prostate, balloon dilation of the prostate, prostatic stents, microwave therapy, laser prostatectomy, transrectal high-intensity focused ultrasound therapy and transurethral needle ablation of the prostate. However, complications may arise through the use of some of these treatments, including retrograde ejaculation, impotence, postoperative urinary tract infection and some urinary incontinence. Non-invasive treatments for BPH include androgen deprivation therapy and the use of 5 $\alpha$ -reductase inhibitors and  $\alpha$ -adrenergic blockers. However, these treatments have proven only minimally to moderately effective for some patients.

Lower urinary tract disorders are particularly problematic for individuals suffering from spinal cord injury. After spinal cord injury, the kidneys continue to make urine, and urine can continue to flow through the ureters and urethra because they are the subject of involuntary neural and muscular control, with the exception of conditions where bladder to smooth muscle dyssnergia is present. By contrast, bladder and sphincter muscles are also subject to voluntary neural and muscular control, meaning that descending input from the brain through the spinal cord drives bladder and sphincter muscles to completely empty the bladder. Following spinal cord injury, such descending input may be disrupted such that individuals may no longer have voluntary control of

their bladder and sphincter muscles. Spinal cord injuries can also disrupt sensory signals that ascend to the brain, preventing such individuals from being able to feel the urge to urinate when their bladder is full.

Following spinal cord injury, the bladder is usually affected in one of two ways. The first is a condition called "spastic" or "reflex" bladder, in which the bladder fills with urine and a reflex automatically triggers the bladder to empty. This usually occurs when the injury is above the T12 level. Individuals with spastic bladder are unable to determine when, or if, the bladder will empty. The second is "flaccid" or "non-reflex" bladder, in which the reflexes of the bladder muscles are absent or slowed. This usually occurs when the injury is below the T12/L1 level. Individuals with flaccid bladder may experience over-distended or stretched bladders and "reflux" of urine through the ureters into the kidneys. Treatment options for these disorders usually include intermittent catheterization, indwelling catheterization, or condom catheterization, but these methods are invasive and frequently inconvenient.

Urinary sphincter muscles may also be affected by spinal cord injuries, resulting in a condition known as "dyssynergia." Dyssynergia involves an inability of urinary sphincter muscles to relax when the bladder contracts, including active contraction in response to bladder contraction, which prevents urine from flowing through the urethra and results in the incomplete emptying of the bladder and "reflux" of urine into the kidneys. Traditional treatments for dyssynergia include medications that have been somewhat inconsistent in their efficacy or surgery.

#### Vulvodynia and Vulvar Vestibulitis

In addition to the lower urinary tract disorders described above, the related genitourinary tract disorders vulvodynia and vulvar vestibulitis have been etiologically and pathologically linked to such lower urinary tract disorders as interstitial cystitis (See Selo-Ojeme *et al.* (2002) *Int. Urogynecol. J. Pelvic Floor Dysfunction* 13: 261-2; Metts (2001) *Am. Fam. Physician* 64: 1199-206; Wesselmann (2001) *World J. Urol.* 19: 180-5; Parsons *et al.* (2001) *Obstet. Gynecol.* 98: 127-32; Heim (2001) *Am. Fam. Physician* 63: 1535-44; Stewart *et al.* (1997) *J. Reprod. Med.* 42: 131-4; Fitzpatrick *et al.* (1993) *Obstet. Gynecol.* 81: 860-2). Vulvar vestibulitis syndrome (herein "vulvar vestibulitis") is a

subtype of vulvodynia. Vulvodynia is a complex gynecologic syndrome characterized by unexplained vulvar pain, sexual dysfunction, and psychological disability. Although the exact prevalence of vulvodynia is unknown, the condition is relatively common. It has been estimated that 1.5 million American women may suffer from some degree of vulvodynia.

The most common subtype of vulvodynia is vulvar vestibulitis (also called "focal vulvitis" and "vestibular adenitis"). Vulvar vestibulitis presents a constellation of symptoms involving and limited to the vulvar vestibule. The criteria for recognizing vulvar vestibulitis include: 1) pain on vestibular touch or attempted vaginal entry; 2) tenderness to Q-tip pressure localized within the vulvar vestibule; 3) physical findings confined to vestibular erythema of various degrees; and 4) an exclusion of other causes for vestibular erythema and tenderness, such as candidiasis (yeast infections) or herpes infections. Other symptoms include itching, swelling and excoriation.

The pain in vulvar vestibulitis may be described as sharp, burning, or a sensation of rawness. In severe cases, dyspareunia (recurrent or persistent genital pain associated with sexual intercourse) totally prohibits sexual intercourse. Pain may also be elicited on tampon insertion, biking, or wearing tight pants. The erythema may be diffuse or focal, and may be localized around the orifices of the vestibular glands or at the fourchette. In addition, patient symptoms may often include itching. Morbidities extend well beyond the local symptoms, with many women undergoing tremendous changes in psychosexual self-image, and can include profound adverse effects on marriages and other important relationships.

Vulvar vestibulitis may be acute or chronic. In one study, an arbitrary cutoff of three months of symptoms was used to distinguish between the acute and chronic forms (Marinoff and Turner, *Am. J. Obstet. Gynecol.* 165:1228-33, 1991). Most clinicians use an arbitrary cutoff of six months to distinguish between the acute and chronic forms. Some investigators have attempted to find a common histopathological aspect to vulvar vestibulitis, but have failed to do so (Pyka *et al.* (1988) *Int. J. Gynecol. Pathol.* 7: 249-57).

The causes of vulvar vestibulitis are multifactorial. Known and suspected causes of the acute form include fungal or bacterial infection (e.g. *Candida*, *Trichomonas*),

chemical irritants (e.g. soaps, douches, sprays), therapeutic agents (e.g. antiseptics, suppositories, creams, 5-fluorouracil methods (e.g. cryosurgery, laser treatment), and allergic drug reactions. In the acute form, treatment of the presumed cause may lead to rapid relief.

Vulvar vestibulitis may become chronic if the cause becomes persistent or recurrent and may persist long after all suspected causes have been treated. Many causes of chronic vulvar vestibulitis are of unknown etiology. Although no direct cause and effect relationship has been shown, it has been suggested that oxalates in the urine, altered vaginal pH, localized peripheral neuropathy, and subclinical viral infections can all contribute to the syndrome. A history of fungal infection is present in most patients who have vulvar vestibulitis, suggesting that recurrent yeast infections may somehow play a role in the initiation of the syndrome. It has been suggested that conditions such as recurrent candidiasis may lead to local changes in the vaginal immune system, including both Th1 and Th2 type responses (Fidel and Sobel, Clin. Microbiol. Reviews 9(3):335-48, 1996).

Because of its multiple causes, and its frequently unknown causes, vulvar vestibulitis can be very difficult to treat. The first-line therapy for vulvar vestibulitis is the treatment of its suspected causes. This includes the pharmacologic treatment of infections and the discontinued use of the irritants and therapeutic agents, local and systemic, that may contribute to the problem. Topical anesthetics, corticosteroids, and sex hormones may provide some symptomatic relief. Further treatments may include dietary modifications, physical therapy and biofeedback, use of topical, oral, or injected therapeutic agents, or surgery. Unfortunately, no single treatment works in all patients. Moreover, many of these approaches involve complex medical procedures, significant costs, and/or undesirable side effects.

Given their relationship to the lower urinary tract disorders described elsewhere herein, the compositions and methods of the present invention are also expected to be useful for treating vulvodynia and/or vulvar vestibulitis. The compositions would comprise a therapeutically effective dose of an  $\alpha_2\delta$  subunit calcium channel modulator, including gabapentin and pregabalin, in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists,

spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. The methods would be accomplished by administering, for example, various compositions and formulations that contain quantities of an  $\alpha_2\delta$  subunit calcium channel modulator and/or other compounds that bind to  $\alpha_2\delta$  subunit-containing calcium channels in combination with one or more compounds with smooth muscle modulatory effects to treat vulvodynia and/or vulvar vestibulitis.

#### Peripheral vs. Central Effects

The mammalian nervous system comprises a central nervous system (CNS, comprising the brain and spinal cord) and a peripheral nervous system (PNS, comprising sympathetic, parasympathetic, sensory, motor, and enteric neurons outside of the brain and spinal cord). Where an active agent according to the present invention is intended to act centrally (i.e., exert its effects via action on neurons in the CNS), the active agent must either be administered directly into the CNS or be capable of bypassing or crossing the blood-brain barrier. The blood-brain barrier is a capillary wall structure that effectively screens out all but selected categories of substances present in the blood, preventing their passage into the CNS. The unique morphologic characteristics of the brain capillaries that make up the blood-brain barrier are: 1) epithelial-like high resistance tight junctions which literally cement all endothelia of brain capillaries together within the blood-brain barrier regions of the CNS; and 2) scanty pinocytosis or transendothelial channels, which are abundant in endothelia of peripheral organs. Due to the unique characteristics of the blood-brain barrier, hydrophilic drugs and peptides that readily gain access to other tissues in the body are barred from entry into the brain or their rates of entry are very low.

The blood-brain barrier can be bypassed effectively by direct infusion of the active agent into the brain, or by intranasal administration or inhalation of formulations suitable for uptake and retrograde transport of the active agent by olfactory neurons. The most common procedure for administration directly into the CNS is the implantation of a catheter into the ventricular system or intrathecal space. Alternatively, the active agent can be modified to enhance its transport across the blood-brain barrier. This generally requires some solubility of the drug in lipids, or other appropriate modification

known to one of skill in the art. For example, the active agent may be truncated, derivatized, latentiated (converted from a hydrophilic drug into a lipid-soluble drug), conjugated to a lipophilic moiety or to a substance that is actively transported across the blood-brain barrier, or modified using standard means known to those skilled in the art. See, for example, Pardridge, Endocrine Reviews 7: 314-330 (1986) and U.S. Pat. No. 4,801,575.

Where an active agent according to the present invention is intended to act exclusively peripherally (i.e., exert its effects via action either on neurons in the PNS or directly on target tissues), it may be desirable to modify the compounds of the present invention such that they will not pass the blood-brain barrier. The principle of blood-brain barrier permeability can therefore be used to design active agents with selective potency for peripheral targets. Generally, a lipid-insoluble drug will not cross the blood-brain barrier, and will not produce effects on the CNS. A basic drug that acts on the nervous system may be altered to produce a selective peripheral effect by quaternization of the drug, which decreases its lipid solubility and makes it virtually unavailable for transfer to the CNS. For example, the charged antimuscarinic drug methscopolamine bromide has peripheral effects while the uncharged antimuscarinic drug scopolamine acts centrally. One of skill in the art can select and modify active agents of the present invention using well-known standard chemical synthetic techniques to add a lipid impermeable functional group such a quaternary amine, sulfate, carboxylate, phosphate, or sulfonium to prevent transport across the blood-brain barrier. Such modifications are by no means the only way in which active agents of the present invention may be modified to be impermeable to the blood-brain barrier; other well known pharmaceutical techniques exist and would be considered to fall within the scope of the present invention.

#### Calcium Channels

Voltage gated calcium channels, also known as voltage dependent calcium channels, are multi-subunit membrane-spanning proteins which permit controlled calcium influx from an extracellular environment into the interior of a cell. Opening and closing (gating) of voltage gated calcium channels is controlled by a voltage sensitive

region of the protein containing charged amino acids that move within an electric field. The movement of these charged groups leads to conformational changes in the structure of the channel resulting in conducting (open/activated) or non-conducting (closed/inactivated) states.

Voltage gated calcium channels are present in a variety of tissues and are implicated in several vital processes in animals. Changes in calcium influx into cells mediated through these calcium channels have been implicated in various human diseases such as epilepsy, stroke, brain trauma, Alzheimer's disease, multi-infarct dementia, other classes of dementia, Korsakoff's disease, neuropathy caused by a viral infection of the brain or spinal cord (e.g., human immunodeficiency viruses, etc.), amyotrophic lateral sclerosis, convulsions, seizures, Huntington's disease, amnesia, or damage to the nervous system resulting from reduced oxygen supply, poison, or other toxic substances (See, e.g., U.S. Pat. No. 5,312,928).

Voltage gated calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey *et al.* (1991) *Curr. Topics Membr.* 39:295-326; and Dunlap *et al.* (1995) *Trends. Neurosci.* 18:89-98). Because there is some overlap in the biophysical properties of the high voltage-activated channels, pharmacological profiles are useful to further distinguish them. L-type channels are sensitive to dihydropyridine agonists and antagonists. N-type channels are blocked by the peptides  $\omega$ -conotoxin GVIA and  $\omega$ -conotoxin MVIIA, peptide toxins from the cone shell mollusks, *Conus geographus* and *Conus magus*, respectively. P-type channels are blocked by the peptide  $\omega$ -agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta*, although some studies have suggested that  $\omega$ -agatoxin IVA also blocks N-type channels (Sidach *et al.* (2000) *J. Neurosci.* 20: 7174-82). A fourth type of high voltage-activated calcium channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather *et al.* (1995) *Neuron* 11:291-303; Stea *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:10576-10580; Bourinet *et al.* (1999) *Nature Neuroscience* 2:407-415).

Voltage gated calcium channels are primarily defined by the combination of different subunits:  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  (see Caterall (2000) *Annu. Rev. Cell. Dev. Biol.* 16:

521-55). Ten types of  $\alpha_1$  subunits, four  $\alpha_2\delta$  complexes, four  $\beta$  subunits, and two  $\gamma$  subunits are known (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; see also Klugbauer et al. (1999) *J. Neurosci.* 19: 684-691).

Based upon the combination of different subunits, calcium channels may be divided into three structurally and functionally related families:  $\text{Ca}_v1$ ,  $\text{Ca}_v2$ , and  $\text{Ca}_v3$  (for reviews, see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Ertel et al. (2000) *Neuron* 25: 533-55). L-type currents are mediated by a  $\text{Ca}_v1$  family of  $\alpha_1$  subunits (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra).  $\text{Ca}_v2$  channels form a distinct family with less than 40% amino acid sequence identity with  $\text{Ca}_v1\alpha_1$  subunits (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra). Cloned  $\text{Ca}_v2.1$  subunits conduct P- or Q-type currents that are inhibited by  $\omega$ -agatoxin IVA (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Sather et al. (1993) *Neuron* 11: 291-303; Stea et al. (1994) *Proc. Natl. Acad. Sci. USA* 91: 10576-80; Bourinet et al. (1999) *Nat. Neurosci.* 2: 407-15).  $\text{Ca}_v2.2$  subunits conduct N-type calcium currents and have a high affinity for  $\omega$ -conotoxin GVIA,  $\omega$ -conotoxin MVIIA, and synthetic versions of these peptides including Ziconotide (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Dubel et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:5058-62; Williams et al. (1992) *Science* 257: 389-95). Cloned  $\text{Ca}_v2.3$  subunits conduct a calcium current known as R-type and are resistant to organic antagonists specific for L-type calcium currents and peptide toxins specific for N-type or P/Q-type currents ((see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Randall et al. (1995) *J. Neurosci.* 15: 2995-3012; Soong et al. (1994) *Science* 260: 1133-36; Zhang et al. (1993) *Neuropharmacology* 32: 1075-88).

#### Acetylcholine Receptors

Acetylcholine is a chemical neurotransmitter in the nervous systems of all animals. "Cholinergic neurotransmission" refers to neurotransmission that involves acetylcholine, and has been implicated in the control of functions as diverse as locomotion, digestion, cardiac rate, "fight or flight" responses, and learning and memory (Salvaterra (Feb. 2000) Acetylcholine. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, <http://www.els.net>). Receptors for acetylcholine are classified into two general categories based on the plant alkaloids that preferentially bind to them: 1)



nicotinic (nicotine binding); or 2) muscarinic (muscarine binding) (See, e.g., Salvaterra, Acetylcholine, supra).

The two general categories of acetylcholine receptors may be further divided into subclasses based upon differences in their pharmacological and electrophysiological properties. For example, nicotinic receptors are composed of a variety of subunits that are used to identify the following subclasses: 1) muscle nicotinic acetylcholine receptors; 2) neuronal nicotinic acetylcholine receptors that do not bind the snake venom  $\alpha$ -bungarotoxin; and 3) neuronal nicotinic acetylcholine receptors that do bind the snake venom  $\alpha$ -bungarotoxin (Dani et al. (July 1999) Nicotinic Acetylcholine Receptors in Neurons. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, <http://www.els.net>; Lindstrom (October 2001) Nicotinic Acetylcholine Receptors. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, <http://www.els.net>). By contrast, muscarinic receptors may be divided into five subclasses, labeled  $M_1$ - $M_5$ , and preferentially couple with specific G-proteins ( $M_1$ ,  $M_3$ , and  $M_5$  with  $G_q$ ;  $M_2$  and  $M_4$  with  $G_i/G_o$ ) (Nathanson (July 1999) Muscarinic Acetylcholine Receptors. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, <http://www.els.net>). In general, antimuscarinic receptors have been implicated in bladder function (See, e.g., Appell (2002) *Cleve. Clin. J. Med.* 69: 761-9; Diouf et al. (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9; Crandall (2001) *J. Womens Health Gend. Based Med.* 10: 735-43; Chapple (2000) *Urology* 55: 33-46).

#### Adrenergic Receptors

Adrenergic receptors are cell-surface receptors for two major catecholamine hormones and neurotransmitters: noradrenaline and adrenaline. (Malbon et al. (Feb. 2000) Adrenergic Receptors. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, <http://www.els.net>). Adrenergic receptors have been implicated in critical physiological processes, including blood pressure control, myocardial and smooth muscle contractility, pulmonary function, metabolism, and central nervous system activity (See, e.g., Malbon et al., Adrenergic Receptors, supra). Two classes of adrenergic receptors have been identified,  $\alpha$  and  $\beta$ , that may be further subdivided into three major families ( $\alpha_1$ ,  $\alpha_2$ , and  $\beta$ ), each with at least three subtypes ( $\alpha_1A$ , B, and, D;

$\alpha 2A$ , B, and C; and  $\beta 1$ ,  $\beta 2$ , and  $\beta 3$ ) based upon their binding characteristics to different agonists and molecular cloning techniques. (See, e.g., Malbon et al., Adrenergic Receptors, supra). It has been shown that  $\beta 3$  adrenergic receptors are expressed in the detrusor muscle, and that the detrusor muscle relaxes with a  $\beta 3$ -agonist (Takeda, M. et al. (1999) *J. Pharmacol. Exp. Ther.* 288: 1367-1373), and in general,  $\beta 3$  adrenergic receptors have been implicated in bladder function (See, e.g., Takeda et al. (2002) *Neurol. Urodyn.* 21: 558-65; Takeda et al. (2000) *J. Pharmacol. Exp. Ther.* 293: 939-45).

#### Spasmolytics

Spasmolytics are compounds that relieve or prevent muscle spasms, especially of smooth muscle. In general, spasmolytics have been implicated as having efficacy in the treatment of bladder disorders (See, e.g., Takeda et al. (2000) *J. Pharmacol. Exp. Ther.* 293: 939-45).

#### Neurokinin Receptors

Tachykinins (TKs) are a family of structurally related peptides that include substance P, neurokinin A (NKA) and neurokinin B (NKB). Neurons are the major source of TKs in the periphery. An important general effect of TKs is neuronal stimulation, but other effects include endothelium-dependent vasodilation, plasma protein extravasation, mast cell recruitment and degranulation and stimulation of inflammatory cells (See Maggi, C. A. (1991) *Gen. Pharmacol.*, 22: 1-24). In general, tachykinin receptors have been implicated in bladder function (See, e.g., Kamo et al. (2000) *Eur. J. Pharmacol.* 401: 235-40 and Omhura et al. (1997) *Urol. Int.* 59: 221-5).

Substance P activates the neurokinin receptor subtype referred to as  $NK_1$ . Substance P is an undecapeptide that is present in sensory nerve terminals. Substance P is known to have multiple actions that produce inflammation and pain in the periphery after C-fiber activation, including vasodilation, plasma extravasation and degranulation of mast cells (Levine, J. D. et al. (1993) *J. Neurosci.* 13: 2273).

Neurokinin A is a peptide which is colocalized in sensory neurons with substance P and which also promotes inflammation and pain. Neurokinin A activates the *specific neurokinin* receptor referred to as  $NK_2$  (Edmonds-Alt, S., et al. (1992) *Life Sci.* 50:

PL101). In the urinary tract, TKs are powerful spasmogens acting through only the NK<sub>2</sub> receptor in the human bladder, as well as the human urethra and ureter (Maggi, C. A. (1991) *Gen. Pharmacol.*, 22: 1-24).

#### Bradykinin Receptors

Bradykinin receptors generally are divided into bradykinin<sub>1</sub> (B<sub>1</sub>) and bradykinin<sub>2</sub> (B<sub>2</sub>) subtypes. Studies have shown that acute peripheral pain and inflammation produced by bradykinin are mediated by the B<sub>2</sub> subtype whereas bradykinin-induced pain in the setting of chronic inflammation is mediated via the B<sub>1</sub> subtype (Perkins, M. N., *et al.* (1993) *Pain* 53: 191-97); Dray, A., *et al.* (1993) *Trends Neurosci.* 16: 99-104). In general, bradykinin receptors have been implicated in bladder function (See, e.g., Meini *et al.* (2000) *Eur. J. Pharmacol.* 388: 177-82 and Belichard *et al.* (1999) *Br. J. Pharmacol.* 128: 213-9).

#### Nitric Oxide

Nitric oxide donors may be included in the present invention particularly for their anti-spasm activity. Nitric oxide (NO) plays a critical role as a molecular mediator of many physiological processes, including vasodilation and regulation of normal vascular tone. The action of NO is implicated in intrinsic local vasodilation mechanisms. NO is the smallest biologically active molecule known and is the mediator of an extraordinary range of physiological processes (Nathan (1994) *Cell* 78: 915-918; Thomas (1997) *Neurosurg. Focus* 3: Article 3). NO is also a known physiologic antagonist of endothelin-1, which is the most potent known mammalian vasoconstrictor, having at least ten times the vasoconstrictor potency of angiotensin II (Yanagisawa *et al.* (1988) *Nature* 332: 411-415; Kasuya *et al.* (1993) *J. Neurosurg.* 79: 892-898; Kobayashi *et al.*, (1991) *Neurosurgery* 28: 673-679). The biological half-life of NO is extremely short (Morris *et al.* (1994) *Am. J. Physiol.* 266: E829-E839; Nathan (1994) *Cell* 78: 915-918). NO accounts entirely for the biological effects of endothelium-derived relaxing factor (EDRF) and is an extremely potent vasodilator that is believed to work through the action of cGMP-dependent protein kinases to effect vasodilation (Henry *et al.* (1993) *FASEB J.* 7: 1124-1134; Nathan (1992) *FASEB J.* 6: 3051-3064; Palmer *et al.*, (1987) *Nature* 327:

524-526; Snyder *et al.* (1992) *Scientific American* 266: 68-77).

Within endothelial cells, an enzyme known as NO synthase (NOS) catalyzes the conversion of L-arginine to NO which acts as a diffusible second messenger and mediates responses in adjacent smooth muscle cells. NO is continuously formed and released by the vascular endothelium under basal conditions which inhibits contractions and controls basal coronary tone and is produced in the endothelium in response to various agonists (such as acetylcholine) and other endothelium dependent vasodilators. Thus, regulation of NOS activity and the resultant levels of NO are key molecular targets controlling vascular tone (Muramatsu *et al.* (1994) *Coron. Artery Dis.* 5: 815-820).

#### Agents

Gamma-aminobutyric acid (GABA) analogs are compounds that are derived from or based on GABA. GABA analogs are either readily available or readily synthesized using methodologies known to those of skill in the art. Exemplary GABA analogs and their salts include gabapentin and pregabalin, and any other GABA analogs as described in U.S. Pat. No. 4,024,175, U.S. Pat. No. 5,563,175, U.S. Patent No. 6,316,638, PCT Publication No. WO 93/23383, Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845, and Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177, which are hereby incorporated by reference. Agents useful in the practice of the invention also include those disclosed in U.S. Application No. 20020111338, cyclic amino acid compounds as disclosed in PCT Publication No. WO 99/08670, compositions disclosed in PCT Publication No. WO 99/08670, U.S. Patent No. 6,342,529, controlled release formulations as disclosed in U.S. Application No. 20020119197 and U.S. Patent No. 5,955,103, and sustained release compounds and formulations as disclosed in PCT Publication No. WO 02/28411, PCT Publication No. WO 02/28881, PCT Publication No. WO 02/28883, PCT Publication No. WO 02/32376, PCT Publication No. WO 02/42414, U.S. Application No. 20020107208, U.S. Application No. 20020151529, and U.S. Application No. 20020098999.

Gabapentin (Neurontin, or 1-(aminomethyl) cyclohexanecarboxylic acid) is an anticonvulsant drug with a high binding affinity for some calcium channel subunits. Although gabapentin was originally developed as a GABA-mimetic compound to treat spasticity, gabapentin has no direct GABAergic action and does not block GABA uptake

or metabolism. (For review, see Rose *et al.* (2002) *Analgesia* 57:451-462). Gabapentin has been found, however, to be an effective treatment for the prevention of partial seizures in patients who are refractory to other anticonvulsant agents (Chadwick (1991) *Gabapentin*, In Pedley T A, Meldrum B S (eds.), *Recent Advances in Epilepsy*, Churchill Livingstone, New York, pp. 211-222). Gabapentin and the related drug pregabalin may interact with the  $\alpha_2\delta$  subunit of calcium channels (Gee *et al.* (1996) *J. Biol. Chem.* 271: 5768-5776).

In addition to its known anticonvulsant effects, gabapentin has been shown to block the tonic phase of nociception induced by formalin and carrageenan, and exerts an inhibitory effect in neuropathic pain models of mechanical hyperalgesia and mechanical/thermal allodynia (Rose *et al.* (2002) *Analgesia* 57: 451-462). Double-blind, placebo-controlled trials have indicated that gabapentin is an effective treatment for painful symptoms associated with diabetic peripheral neuropathy, post-herpetic neuralgia, and neuropathic pain (see, e.g., Backonja *et al.* (1998) *JAMA* 280:1831-1836; Mellegers *et al.* (2001) *Clin. J. Pain* 17:284-95).

Pregabalin, (S)-(3-aminomethyl)-5-methylhexanoic acid or (S)-isobutyl GABA, is another GABA analog whose use as an anticonvulsant has been explored (Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845). Pregabalin has been shown to possess even higher binding affinity for the  $\alpha_2\delta$  subunit of calcium channels than gabapentin (Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177).

Other GABA analogs which display binding affinity to the  $\alpha_2\delta$  subunit of calcium channels include, without limitation, cis-(1S,3R)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, cis-(1R,3S)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, 1 $\alpha$ ,3 $\alpha$ ,5 $\alpha$ -(1-aminomethyl)-(3,5-dimethylcyclohexane)acetic acid, (9-(aminomethyl)bicyclo[3.3.1]non-9-yl)acetic acid, and (7-(aminomethyl)bicyclo[2.2.1]hept-7-yl)acetic acid (Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845; Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177).

Other agents useful in the present invention include any compound that binds to the  $\alpha_2\delta$  subunit of a calcium channel. Compounds that have been identified as modulators of calcium channels include, but are not limited to those described in US Patent No. 6,316,638, US Patent No. 6,492,375, US Patent No. 6,294,533, US Patent No.

6,011,035, US Patent No. 6,387,897, US Patent No. 6,310,059, US Patent No. 6,294,533, US Patent No. 6,267,945, PCT Publication No. WO01/49670, PCT Publication No. WO01/46166, and PCT Publication No. WO01/45709. The identification of which of these compounds have a binding affinity for the  $\alpha_2\delta$  subunit of calcium channels can be determined by performing  $\alpha_2\delta$  binding affinity studies as described by Gee *et al.* (Gee *et al.* (1996) *J. Biol. Chem.* 271:5768-5776). The identification of still further compounds, including other GABA analogs, that have a binding affinity for the  $\alpha_2\delta$  subunit of calcium channels can also be determined by performing  $\alpha_2\delta$  binding affinity studies as described by Gee *et al.* (Gee *et al.* (1996) *J. Biol. Chem.* 271:5768-5776).

Other agents useful in the present invention include any anticholinergic agent, specifically, any antimuscarinic agent. Compounds that have been identified as antimuscarinic agents and are useful in the present invention include, but are not limited to:

- a. Darifenacin (Daryon<sup>®</sup>);
- b. YM-905 (solifenacin succinate);
- c. Oxybutynin (Ditropan<sup>®</sup>);
- d. S-Oxybutynin;
- e. N-desethyl-oxybutynin;
- f. tolterodine (Detrol<sup>®</sup>);
- g. Trospium (Uraplex<sup>®</sup>, Spasmex<sup>®</sup>);
- h. Propiverine (Detrunorm<sup>®</sup>);
- i. Propantheline bromide (Pro-Banthine<sup>®</sup>);
- j. Hyoscyamine sulfate (Levsin<sup>®</sup>, Cystospaz<sup>®</sup>);
- k. Dicyclomine hydrochloride (Bentyl<sup>®</sup>);
- l. Flavoxate hydrochloride (Urispas<sup>®</sup>);
- m. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
- n. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
- o. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;

- p. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate;
- q. 1-methyl-4-piperidyl diphenylpropoxyacetate;
- r. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
- s. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
- t. pirenzepine;
- u. methoctramine;
- v. 4-diphenylacetoxy-N-methyl piperidine methiodide;
- w. tropicamide;
- x. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and
- y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

The identification of further compounds that have antimuscarinic activity and would therefore be useful in the present invention can be determined by performing muscarinic receptor binding specificity studies as described by Nilvebrant (2002) *Pharmacol. Toxicol.* 90: 260-7 or cystometry studies as described by Modiri *et al.* (2002) *Urology* 59: 963-8.

Other agents useful in the present invention include any  $\beta 3$  adrenergic agonist agent. Compounds that have been identified as  $\beta 3$  adrenergic agonist agents and are useful in the present invention include, but are not limited to:

- a. TT-138 and phenylethanolamine compounds as disclosed in US Patent No. 6,069,176, PCT Publication No. WO 97/15549 and available from Mitsubishi Pharma Corp.;
- b. FR-149174 and propanolamine derivatives as disclosed in US Patent Nos. 6,495,546 and 6,391,915 and available from Fujisawa Pharmaceutical Co.;
- c. KUC-7483, available from Kissei Pharmaceutical Co.,

- d. 4'-hydroxynorephedrine derivatives such as 2- 2-chloro-4-(2-(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino)ethyl)phenoxy acetic acid as disclosed in Tanaka *et al.* (2003) *J. Med. Chem.* 46: 105-12;
- e. 2-amino-1-phenylethanol compounds, such as BRL35135 ((R\*R\*)-(+,-)-[4-[2-[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]phenoxy]acetic acid methyl ester hydrobromide salt as disclosed in Japanese Patent Publication No. 26744 of 1988 and European Patent Publication No. 23385), and SR58611A ((RS)-N-(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl)-2-(3-chlorophenyl)-2-hydroxyethanamine hydrochloride as disclosed in Japanese Laid-open Patent Publication No. 66152 of 1989 and European Laid-open Patent Publication No. 255415);
- f. GS 332 (Sodium (2R)-[3-[3-[2-(3 Chlorophenyl)-2-hydroxyethylamino]cyclohexyl]phenoxy]acetate) as disclosed in Iizuka *et al.* (1998) *J. Smooth Muscle Res.* 34: 139-49;
- g. BRL-37,344 (4-[-(2-hydroxy-(3-chlorophenyl) ethyl)-amino]propyl]phenoxyacetate) as disclosed in Tsujii *et al.* (1998) *Physiol. Behav.* 63: 723-8 and available from Glaxosmithkline;
- h. BRL-26830A as disclosed in Takahashi *et al.* (1992) *Jpn Circ. J.* 56: 936-42 and available from Glaxosmithkline;
- i. CGP 12177 (4-[3-t-butylamino-2-hydroxypropoxy]benzimidazol-2-one) (a  $\beta$ 1/ $\beta$ 2 adrenergic antagonist reported to act as an agonist for the  $\beta$ 3 adrenergic receptor) as described in Tavernier *et al.* (1992) *J. Pharmacol. Exp. Ther.* 263: 1083-90 and available from Ciba-Geigy;
- j. CL 316243 (R,R-5-[2-[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-



dicarboxylate) as disclosed in Berlan *et al.* (1994) *J.*

*Pharmacol. Exp. Ther.* 268: 1444-51;

- k. Compounds having  $\beta 3$  adrenergic agonist activity as disclosed in US Patent Application 20030018061;
- l. ICI 215,001 HCl ((*S*)-4-[2-Hydroxy-3-phenoxypropylaminoethoxy]phenoxyacetic acid hydrochloride) as disclosed in Howe (1993) *Drugs Future* 18: 529 and available from AstraZeneca/ICI Labs;
- m. ZD 7114 HCl (ICI D7114; (*S*)-4-[2-Hydroxy-3-phenoxypropylaminoethoxy]-*N*-(2-methoxyethyl)phenoxyacetamide HCl) as disclosed in Howe (1993) *Drugs Future* 18: 529 and available from AstraZeneca/ICI Labs;
- n. Pindolol (1-(1*H*-Indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol) as disclosed in Blin *et al* (1994) *Mol.Pharmacol.* 44: 1094;
- o. (*S*)-(-)-Pindolol ((*S*)-1-(1*H*-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol) as disclosed in Walter *et al* (1984) *Naunyn-Schmied.Arch.Pharmacol.* 327: 159 and Kalkman (1989) *Eur.J.Pharmacol.* 173: 121;
- p. SR 59230A HCl (1-(2-Ethylphenoxy)-3-[[1*S*]-1,2,3,4-tetrahydro-1-naphthalenyl]amino]-(2*S*)-2-propanol hydrochloride) as disclosed in Manara *et al.* (1995) *Pharmacol. Comm.* 6: 253 and Manara *et al.* (1996) *Br. J. Pharmacol.* 117: 435 and available from Sanofi-Midy; and
- q. SR 58611 (*N*[2*s*]7-carb-ethoxymethoxy-1,2,3,4-tetrahydronaphth]-(2*r*)-2-hydroxy-2(3-chlorophenyl) ethamine hydrochloride) as disclosed in Gauthier *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290: 687-693 and available from Sanofi Research.

The identification of further compounds that have  $\beta_3$  adrenergic agonist activity and would therefore be useful in the present invention can be determined by performing radioligand binding assays and/or contractility studies as described by Zilberfarb *et al.* (1997) *J. Cell Sci.* 110: 801-807; Takeda *et al.* (1999) *J. Pharmacol. Exp. Ther.* 288: 1367-1373; and Gauthier *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290: 687-693.

Other agents useful in the present invention include any spasmolytic agent. Compounds that have been identified as spasmolytic agents and are useful in the present invention include, but are not limited to:

- a.  $\alpha$ - $\alpha$ -diphenylacetic acid-4-(N-methyl-piperidyl) esters as disclosed in US Patent No. 5,897,875;
- b. Human and porcine spasmolytic polypeptides in glycosylated form and variants thereof as disclosed in US Patent No. 5,783,416;
- c. Dioxazocine derivatives as disclosed in US Patent No. 4,965,259;
- d. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkyl norscopine ethers as disclosed in US Patent No. 4,608,377;
- e. Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones as disclosed in US Patent No. 4,594,190;
- f. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts as disclosed in US Patent No. 4,558,054;
- g. Pancreatic spasmolytic polypeptides as disclosed in US Patent No. 4,370,317;
- h. Triazinones as disclosed in US Patent No. 4,203,983;
- i. 2-(4-Biphenyl)-N-(2-diethylamino alkyl)propionamide as disclosed in US Patent No. 4,185,124;
- j. Piperazino-pyrimidines as disclosed in US Patent No. 4,166,852;

- k. Aralkylamino carboxylic acids as disclosed in US Patent No. 4,163,060;
- l. Aralkylamino sulfones as disclosed in US Patent No. 4,034,103;
- m. Smooth muscle spasmolytic agents as disclosed in US Patent No. 6,207,852; and
- n. papaverine.

The identification of further compounds that have spasmolytic activity and would therefore be useful in the present invention can be determined by performing bladder strip contractility studies as described in US Patent No. 6,207,852; Noronha-Blob *et al.* (1991) *J. Pharmacol. Exp. Ther.* 256: 562-567; and/or Kachur *et al.* (1988) *J. Pharmacol. Exp. Ther.* 247: 867-872.

Other agents useful in the present invention include any neurokinin receptor antagonist agent. Suitable neurokinin receptor antagonists for use in the present invention that act on the NK<sub>1</sub> receptor include, but are not limited to: 1-imino-2-(2-methoxy-phenyl)-ethyl-7,7-diphenyl-4-perhydroisoindolone(3aR,7aR) ("RP 67580"); 2S,3S-cis-3-(2-methoxybenzylamino)-2-benzhydrylquinuclidine ("CP 96,345"); and (aR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthyridine-6,13-dione("TAK-637"). Suitable neurokinin receptor antagonists for use in the present invention that act on the NK<sub>2</sub> receptor include but are not limited to: ((S)-N-methyl-N-4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide ("SR 48968"); Met-Asp-Trp-Phe-Dap-Leu ("MEN 10,627"); and cyc(Gln-Trp-Phe-Gly-Leu-Met) ("L 659,877").

The identification of further compounds that have neurokinin receptor antagonist activity and would therefore be useful in the present invention can be determined by performing binding assay studies as described in Hopkins *et al.* (1991) *Biochem. Biophys. Res. Comm.* 180: 1110-1117; and Aharony *et al.* (1994) *Mol. Pharmacol.* 45: 9-19.

Other agents useful in the present invention include any bradykinin receptor antagonist agent. Suitable bradykinin receptor antagonists for use in the present invention that act on the B<sub>1</sub> receptor include but are not limited to: des-arg<sup>10</sup>HOE 140

(available from Hoechst Pharmaceuticals) and des-Arg<sup>9</sup>bradykinin (DABK). Suitable bradykinin receptor antagonists for use in the present invention that act on the B<sub>2</sub> receptor include but are not limited to: D-Phe<sup>7</sup>-BK; D-Arg-(Hyp<sup>3</sup>-Thi<sup>5,8</sup>-D-Phe<sup>7</sup>)-BK ("NPC 349"); D-Arg-(Hyp<sup>3</sup>-D-Phe<sup>7</sup>)-BK ("NPC 567"); D-Arg-(Hyp<sup>3</sup>-Thi<sup>5</sup>-D-Tic<sup>7</sup>-Oic<sup>8</sup>)-BK ("HOE 140"); H-DArg-Arg-Pro-Hyp-Gly-Thi-c(Dab-DTic-Oic-Arg)c(7gamma-10alpha)("MEN11270"); H-DArg-Arg-Pro-Hyp-Gly-Thi-Ser-DTic-Oic-Arg-OH("Icatibant"); (E)-3-(6-acetamido-3-pyridyl)-N-[N-[2, 4-dichloro-3-[(2-methyl-8-quinoliny) oxymethyl] phenyl]-N-methylaminocarbonylmethyl]acrylamide ("FR173567"); and WIN 64338.

These compounds are more fully described in Perkins, M. N., *et. al.*, *Pain, supra*; Dray, A., *et. al.*, *Trends Neurosci., supra*; and Meini *et al.* (2000) *Eur. J. Pharmacol.* 388: 177-82. The identification of further compounds that have bradykinin receptor antagonist activity and would therefore be useful in the present invention can be determined by performing binding assay studies as described in Manning *et al.* (1986) *J. Pharmacol. Exp. Ther.* 237: 504 and US Patent No. 5,686,565.

Other agents useful in the present invention include any nitric oxide donor agent. Suitable nitric oxide donors for the practice of the present invention include but are not limited to:

- a. Nitroglycerin;
- b. Sodium nitroprusside;
- c. FK 409 (NOR-3);
- d. FR 144420 (NOR-4);
- e. 3-morpholinosydnonimine;
- f. Linsidomine chlorohydrate ("SIN-1");
- g. S-nitroso-N-acetylpencillamine ("SNAP");
- h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
- i. NCX 4016 (available from NicOx S.A.);
- j. NCX 701 (available from NicOx S.A.);
- k. NCX 1022 (available from NicOx S.A.);
- l. HCT 1026 (available from NicOx S.A.);

- m. NCX 1015 (available from NicOx S.A.);
- n. NCX 950 (available from NicOx S.A.);
- o. NCX 1000 (available from NicOx S.A.);
- p. NCX 1020 (available from NicOx S.A.);
- q. AZD 4717 (available from NicOx S.A.);
- r. NCX 1510/NCX 1512 (available from NicOx S.A.);
- s. NCX 2216 (available from NicOx S.A.);
- t. NCX 4040 (available from NicOx S.A.);
- u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
- v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
- w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
- x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
- y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
- z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;
- aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
- bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
- cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;
- dd. Nitric oxide donors as disclosed in U.S. Patent No. 5,714,511;
- ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911;
- and
- ff. Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

The identification of further compounds that have nitric oxide donor activity and would therefore be useful in the present invention can be determined by release profile and/or induced vasospasm studies as described in US Patent Nos. 6,451,337 and 6,358,536, as well as Moon (2002) *IBJU Int.* 89: 942-9 and Fathian-Sabet *et al.* (2001) *J. Urol.* 165: 1724-9.

### Formulations

Formulations of the present invention may include, but are not limited to, continuous, as needed, short-term, rapid-offset, controlled release, sustained release, delayed release, and pulsatile release formulations.

Compositions of the invention comprise  $\alpha_2\delta$  subunit calcium channel modulators or other compounds that bind to the  $\alpha_2\delta$  calcium channel subunit in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. The compositions are administered in therapeutically effective amounts to a patient in need thereof for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. It is recognized that the compositions may be administered by any means of administration as long as an effective amount for the treatment of painful and non-painful symptoms associated with lower urinary tract disorders in normal and spinal cord injured patients is delivered.

Any of the active agents may be administered in the form of a salt, ester, amide, prodrug, active metabolite, derivative, or the like, provided that the salt, ester, amide, prodrug or derivative is suitable pharmacologically, i.e., effective in the present method. Salts, esters, amides, prodrugs and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience, 1992). For example, acid addition salts are prepared from the free base using conventional methodology, and involves reaction with a suitable acid. Suitable acids for preparing acid addition salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Particularly preferred acid addition salts of the active

agents herein are salts prepared with organic acids. Conversely, preparation of basic salts of acid moieties which may be present on an active agent are prepared in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like.

Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups that may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, i.e., moieties that are derived from carboxylic acids of the formula  $\text{RCOOH}$  where R is alkyl, and preferably is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Amides and prodrugs may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs are typically prepared by covalent attachment of a moiety, which results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature. In addition, chiral active agents may be in isomerically pure form, or they may be administered as a racemic mixture of isomers.

#### Pharmaceutical Compositions and Dosage Forms

Suitable compositions and dosage forms include tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, transdermal patches, gels, powders, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. Further, those of ordinary skill in the art can readily deduce that suitable formulations involving these compositions and dosage forms, including those formulations as described elsewhere herein.

### *Oral Dosage Forms*

Oral dosage forms include tablets, capsules, caplets, solutions, suspensions and/or syrups, and may also comprise a plurality of granules, beads, powders or pellets that may or may not be encapsulated. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts, e.g., in Remington: The Science and Practice of Pharmacy, supra). Tablets and capsules represent the most convenient oral dosage forms, in which case solid pharmaceutical carriers are employed.

Tablets may be manufactured using standard tablet processing procedures and equipment. One method for forming tablets is by direct compression of a powdered, crystalline or granular composition containing the active agent(s), alone or in combination with one or more carriers, additives, or the like. As an alternative to direct compression, tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist or otherwise tractable material; however, compression and granulation techniques are preferred.

In addition to the active agent(s), then, tablets prepared for oral administration using the method of the invention will generally contain other materials such as binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, preservatives, coloring agents, flavoring agents and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, propylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Diluents are typically necessary to increase bulk so that a practical size tablet is ultimately provided. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma, glycerin, magnesium



stearate, calcium stearate, and stearic acid. Stearates, if present, preferably represent at no more than approximately 2 wt. % of the drug-containing core. Disintegrants are used to facilitate disintegration of the tablet, and are generally starches, clays, celluloses, algin, gums or crosslinked polymers. Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride and sorbitol. Stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents.

The dosage form may also be a capsule, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. (See, for e.g., Remington: The Science and Practice of Pharmacy, supra), which describes materials and methods for preparing encapsulated pharmaceuticals. If the active agent-containing composition is present within the capsule in liquid form, a liquid carrier is necessary to dissolve the active agent(s). The carrier must be compatible with the capsule material and all components of the pharmaceutical composition, and must be suitable for ingestion.

Solid dosage forms, whether tablets, capsules, caplets, or particulates, may, if desired, be coated so as to provide for delayed release. Dosage forms with delayed release coatings may be manufactured using standard coating procedures and equipment. Such procedures are known to those skilled in the art and described in the pertinent texts (See, for e.g., Remington: The Science and Practice of Pharmacy, supra). Generally, after preparation of the solid dosage form, a delayed release coating composition is applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. Delayed release coating compositions comprise a polymeric material, e.g., cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose

acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, polymers and copolymers formed from acrylic acid, methacrylic acid, and/or esters thereof.

Sustained release dosage forms provide for drug release over an extended time period, and may or may not be delayed release. Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms are formulated by dispersing a drug within a matrix of a gradually bioerodible (hydrolyzable) material such as an insoluble plastic, a hydrophilic polymer, or a fatty compound, or by coating a solid, drug-containing dosage form with such a material. Insoluble plastic matrices may be comprised of, for example, polyvinyl chloride or polyethylene. Hydrophilic polymers useful for providing a sustained release coating or matrix cellulosic polymers include, without limitation: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, hydroxypropylcellulose phthalate, cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, with a terpolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride (sold under the tradename Eudragit RS) preferred; vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate. Fatty compounds for use as a sustained release matrix material include, but are not limited to, waxes generally (e.g., carnauba wax) and glyceryl tristearate.

#### *Transmucosal Compositions and Dosage Forms*

Although the present compositions may be administered orally, other modes of administration are suitable as well. For example, transmucosal administration may be advantageously employed. Transmucosal administration is carried out using any type of

formulation or dosage unit suitable for application to mucosal tissue. For example, the selected active agent may be administered to the buccal mucosa in an adhesive tablet or patch, sublingually administered by placing a solid dosage form under the tongue, lingually administered by placing a solid dosage form on the tongue, administered nasally as droplets or a nasal spray, administered by inhalation of an aerosol formulation, a non-aerosol liquid formulation, or a dry powder, placed within or near the rectum ("transrectal" formulations), or administered to the urethra as a suppository, ointment, or the like.

Preferred buccal dosage forms will typically comprise a therapeutically effective amount of an active agent and a bioerodible (hydrolyzable) polymeric carrier that may also serve to adhere the dosage form to the buccal mucosa. The buccal dosage unit is fabricated so as to erode over a predetermined time period, wherein drug delivery is provided essentially throughout. The time period is typically in the range of from about 1 hour to about 72 hours. Preferred buccal delivery preferably occurs over a time period of from about 2 hours to about 24 hours. Buccal drug delivery for short term use should preferably occur over a time period of from about 2 hours to about 8 hours, more preferably over a time period of from about 3 hours to about 4 hours. As needed buccal drug delivery preferably will occur over a time period of from about 1 hour to about 12 hours, more preferably from about 2 hours to about 8 hours, most preferably from about 3 hours to about 6 hours. Sustained buccal drug delivery will preferably occur over a time period of from about 6 hours to about 72 hours, more preferably from about 12 hours to about 48 hours, most preferably from about 24 hours to about 48 hours. Buccal drug delivery, as will be appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver.

The "therapeutically effective amount" of the active agent in the buccal dosage unit will of course depend on the potency of the agent and the intended dosage, which, in turn, is dependent on the particular individual undergoing treatment, the specific indication, and the like. The buccal dosage unit will generally contain from about 1.0 wt. % to about 60 wt. % active agent, preferably on the order of from about 1 wt. % to about

30 wt. % active agent. With regard to the bioerodible (hydrolyzable) polymeric carrier, it will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with the active agents to be administered and any other components of the buccal dosage unit. Generally, the polymeric carrier comprises a hydrophilic (water-soluble and water-swellaable) polymer that adheres to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B. F. Goodrich, is one such polymer). Other suitable polymers include, but are not limited to: hydrolyzed polyvinylalcohol; polyethylene oxides (e.g., Sentry Polyox® water soluble resins, available from Union Carbide); polyacrylates (e.g., Gantrez®, which may be obtained from GAF); vinyl polymers and copolymers; polyvinylpyrrolidone; dextran; guar gum; pectins; starches; and cellulosic polymers such as hydroxypropyl methylcellulose, (e.g., Methocel®, which may be obtained from the Dow Chemical Company), hydroxypropyl cellulose (e.g., Klucel®, which may also be obtained from Dow), hydroxypropyl cellulose ethers (see, e.g., U.S. Pat. No. 4,704,285 to Alderman), hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, and the like.

Other components may also be incorporated into the buccal dosage forms described herein. The additional components include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like. Examples of disintegrants that may be used include, but are not limited to, cross-linked polyvinylpyrrolidones, such as crospovidone (e.g., Polyplasdone® XL, which may be obtained from GAF), cross-linked carboxylic methylcelluloses, such as croscarmellose (e.g., Ac-di-sol®, which may be obtained from FMC), alginic acid, and sodium carboxymethyl starches (e.g., Explotab®, which may be obtained from Edward Medell Co., Inc.), methylcellulose, agar bentonite and alginic acid. Suitable diluents are those which are generally useful in pharmaceutical formulations prepared using compression techniques, e.g., dicalcium phosphate dihydrate (e.g., Di-Tab®, which may be obtained from Stauffer), sugars that have been processed by cocrystallization with dextrin (e.g., co-crystallized sucrose and dextrin such as Di-Pak®, which may be obtained from

Amstar), calcium phosphate, cellulose, kaolin, mannitol, sodium chloride, dry starch, powdered sugar and the like. Binders, if used, are those that enhance adhesion. Examples of such binders include, but are not limited to, starch, gelatin and sugars such as sucrose, dextrose, molasses, and lactose. Particularly preferred lubricants are stearates and stearic acid, and an optimal lubricant is magnesium stearate.

Sublingual and lingual dosage forms include tablets, creams, ointments, lozenges, pastes, and any other solid dosage form where the active ingredient is admixed into a disintegrable matrix. The tablet, cream, ointment or paste for sublingual or lingual delivery comprises a therapeutically effective amount of the selected active agent and one or more conventional nontoxic carriers suitable for sublingual or lingual drug administration. The sublingual and lingual dosage forms of the present invention can be manufactured using conventional processes. The sublingual and lingual dosage units are fabricated to disintegrate rapidly. The time period for complete disintegration of the dosage unit is typically in the range of from about 10 seconds to about 30 minutes, and optimally is less than 5 minutes.

Other components may also be incorporated into the sublingual and lingual dosage forms described herein. The additional components include, but are not limited to binders, disintegrants, wetting agents, lubricants, and the like. Examples of binders that may be used include water, ethanol, polyvinylpyrrolidone; starch solution gelatin solution, and the like. Suitable disintegrants include dry starch, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic monoglyceride, lactose, and the like. Wetting agents, if used, include glycerin, starches, and the like. Particularly preferred lubricants are stearates and polyethylene glycol. Additional components that may be incorporated into sublingual and lingual dosage forms are known, or will be apparent, to those skilled in this art (See, e.g., Remington: The Science and Practice of Pharmacy, supra).

For transurethral administration, the formulation comprises a urethral dosage form containing the active agent and one or more selected carriers or excipients, such as water, silicone, waxes, petroleum jelly, polyethylene glycol ("PEG"), propylene glycol ("PG"), liposomes, sugars such as mannitol and lactose, and/or a variety of other materials, with polyethylene glycol and derivatives thereof particularly preferred.

Depending on the particular active agent administered, it may be desirable to incorporate a transurethral permeation enhancer in the urethral dosage form. Examples of suitable transurethral permeation enhancers include dimethylsulfoxide ("DMSO"), dimethyl formamide ("DMF"), N, N-dimethylacetamide ("DMA"), decylmethylsulfoxide ("C<sub>10</sub> MSO"), polyethylene glycol monolaurate ("PEGML"), glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone® from Nelson Research & Development Co., Irvine, Calif.), SEPA® (available from Macrochem Co., Lexington, Mass.), surfactants as discussed above, including, for example, Tergitol®, Nonoxynol-9® and TWEEN-80®, and lower alkanols such as ethanol.

Transurethral drug administration, as explained in U.S. Pat. Nos. 5,242,391, 5,474,535, 5,686,093 and 5,773,020, can be carried out in a number of different ways using a variety of urethral dosage forms. For example, the drug can be introduced into the urethra from a flexible tube, squeeze bottle, pump or aerosol spray. The drug may also be contained in coatings, pellets or suppositories that are absorbed, melted or bioeroded in the urethra. In certain embodiments, the drug is included in a coating on the exterior surface of a penile insert. It is preferred, although not essential, that the drug be delivered from at least about 3 cm into the urethra, and preferably from at least about 7 cm into the urethra. Generally, delivery from at least about 3 cm to about 8 cm into the urethra will provide effective results in conjunction with the present method.

Urethral suppository formulations containing PEG or a PEG derivative may be conveniently formulated using conventional techniques, e.g., compression molding, heat molding or the like, as will be appreciated by those skilled in the art and as described in the pertinent literature and pharmaceutical texts. (See, e.g., Remington: The Science and Practice of Pharmacy, supra), which discloses typical methods of preparing pharmaceutical compositions in the form of urethral suppositories. The PEG or PEG derivative preferably has a molecular weight in the range of from about 200 to about 2,500 g/mol, more preferably in the range of from about 1,000 to about 2,000 g/mol. Suitable polyethylene glycol derivatives include polyethylene glycol fatty acid esters, for example, polyethylene glycol monostearate, polyethylene glycol sorbitan esters, e.g., polysorbates, and the like. Depending on the particular active agent, it may also be

preferred that urethral suppositories contain one or more solubilizing agents effective to increase the solubility of the active agent in the PEG or other transurethral vehicle.

It may be desirable to deliver the active agent in a urethral dosage form that provides for controlled or sustained release of the agent. In such a case, the dosage form comprises a biocompatible, biodegradable material, typically a biodegradable polymer. Examples of such polymers include polyesters, polyalkylcyanoacrylates, polyorthoesters, polyanhydrides, albumin, gelatin and starch. As explained, for example, in PCT Publication No. WO 96/40054, these and other polymers can be used to provide biodegradable microparticles that enable controlled and sustained drug release, in turn minimizing the required dosing frequency.

The urethral dosage form will preferably comprise a suppository that is on the order of from about 2 to about 20 mm in length, preferably from about 5 to about 10 mm in length, and less than about 5 mm in width, preferably less than about 2 mm in width. The weight of the suppository will typically be in the range of from about 1 mg to about 100 mg, preferably in the range of from about 1 mg to about 50 mg. However, it will be appreciated by those skilled in the art that the size of the suppository can and will vary, depending on the potency of the drug, the nature of the formulation, and other factors.

Transurethral drug delivery may involve an "active" delivery mechanism such as iontophoresis, electroporation or phonophoresis. Devices and methods for delivering drugs in this way are well known in the art. Iontophoretically assisted drug delivery is, for example, described in PCT Publication No. WO 96/40054, cited above. Briefly, the active agent is driven through the urethral wall by means of an electric current passed from an external electrode to a second electrode contained within or affixed to a urethral probe.

Preferred transrectal dosage forms include rectal suppositories, creams, ointments, and liquid formulations (enemas). The suppository, cream, ointment or liquid formulation for transrectal delivery comprises a therapeutically effective amount of the selected phosphodiesterase inhibitor and one or more conventional nontoxic carriers suitable for transrectal drug administration. The transrectal dosage forms of the present invention can be manufactured using conventional processes. The transrectal dosage unit can be fabricated to disintegrate rapidly or over a period of several hours. The time period

for complete disintegration is preferably in the range of from about 10 minutes to about 6 hours, and optimally is less than about 3 hours.

Other components may also be incorporated into the transrectal dosage forms described herein. The additional components include, but are not limited to, stiffening agents, antioxidants, preservatives, and the like. Examples of stiffening agents that may be used include, for example, paraffin, white wax and yellow wax. Preferred antioxidants, if used, include sodium bisulfite and sodium metabisulfite.

The active agents may also be administered intranasally or by inhalation. Compositions for intranasal administration are generally liquid formulations for administration as a spray or in the form of drops, although powder formulations for intranasal administration, e.g., insufflations, are also known, as are nasal gels, creams, pastes or ointments. For liquid formulations, the active agent can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from about pH 6.0 to about pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. Furthermore, various devices are available in the art for the generation of drops, droplets and sprays, including droppers, squeeze bottles, and manually and electrically powered intranasal pump dispensers. Active agent containing intranasal carriers may also include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 6500 cps, or greater, depending on the desired sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington: The Science and Practice of Pharmacy, supra). Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. Formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier (e.g., propellant) or a dispersion aerosol in which the



active agent is suspended or dispersed throughout a carrier and an optional solvent. Non-aerosol formulations for inhalation may take the form of a liquid, typically an aqueous suspension, although aqueous solutions may be used as well. In such a case, the carrier is typically a sodium chloride solution having a concentration such that the formulation is isotonic relative to normal body fluid. In addition to the carrier, the liquid formulations may contain water and/or excipients including an antimicrobial preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, phenylethyl alcohol, thimerosal and combinations thereof), a buffering agent (e.g., citric acid, potassium metaphosphate, potassium phosphate, sodium acetate, sodium citrate, and combinations thereof), a surfactant (e.g., polysorbate 80, sodium lauryl sulfate, sorbitan monopalmitate and combinations thereof), and/or a suspending agent (e.g., agar, bentonite, microcrystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, tragacanth, veegum and combinations thereof). Non-aerosol formulations for inhalation may also comprise dry powder formulations, particularly insufflations in which the powder has an average particle size of from about 0.1  $\mu\text{m}$  to about 50  $\mu\text{m}$ , preferably from about 1  $\mu\text{m}$  to about 25  $\mu\text{m}$ .

### *Topical Formulations*

Topical formulations may be in any form suitable for application to the body surface, and may comprise, for example, an ointment, cream, gel, lotion, solution, paste or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. Preferred topical formulations herein are ointments, creams and gels.

Ointments, as is well known in the art of pharmaceutical formulation, are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, preferably, will provide for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing. As explained in Remington: The Science and Practice of Pharmacy, supra, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for

example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight (See, e.g., Remington: The Science and Practice of Pharmacy, supra).

Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant.

As will be appreciated by those working in the field of pharmaceutical formulation, gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the carrier liquid, which is typically aqueous, but also, preferably, contain an alcohol and, optionally, an oil. Preferred "organic macromolecules," i.e., gelling agents, are crosslinked acrylic acid polymers such as the "carbomer" family of polymers, e.g., carboxypolyalkylenes that may be obtained commercially under the Carbopol® trademark. Also preferred are hydrophilic polymers such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers and polyvinylalcohol; cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

Various additives, known to those skilled in the art, may be included in the topical formulations. For example, solubilizers may be used to solubilize certain active agents.

For those drugs having an unusually low rate of permeation through the skin or mucosal tissue, it may be desirable to include a permeation enhancer in the formulation; suitable enhancers are as described elsewhere herein.

#### *Transdermal Administration*

The compounds of the invention may also be administered through the skin or mucosal tissue using conventional transdermal drug delivery systems, wherein the agent is contained within a laminated structure (typically referred to as a transdermal "patch") that serves as a drug delivery device to be affixed to the skin. Transdermal drug delivery may involve passive diffusion or it may be facilitated using electrotransport, e.g., iontophoresis. In a typical transdermal "patch," the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one type of patch, referred to as a "monolithic" system, the reservoir is comprised of a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form.

The backing layer in these laminates, which serves as the upper surface of the device, functions as the primary structural element of the laminated structure and provides the device with much of its flexibility. The material selected for the backing material should be selected so that it is substantially impermeable to the active agent and any other materials that are present, the backing is preferably made of a sheet or film of a flexible elastomeric material. Examples of polymers that are suitable for the backing layer include polyethylene, polypropylene, polyesters, and the like.

During storage and prior to use, the laminated structure includes a release liner. Immediately prior to use, this layer is removed from the device to expose the basal surface thereof, either the drug reservoir or a separate contact adhesive layer, so that the

system may be affixed to the skin. The release liner should be made from a drug/vehicle impermeable material.

Transdermal drug delivery systems may in addition contain a skin permeation enhancer. That is, because the inherent permeability of the skin to some drugs may be too low to allow therapeutic levels of the drug to pass through a reasonably sized area of unbroken skin, it is necessary to coadminister a skin permeation enhancer with such drugs. Suitable enhancers are well known in the art and include, for example, those enhancers listed above in transmucosal compositions.

#### *Parenteral Administration*

Parenteral administration, if used, is generally characterized by injection, including intramuscular, intraperitoneal, intravenous (IV) and subcutaneous injection. Injectable formulations can be prepared in conventional forms, either as liquid solutions or suspensions; solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable formulation may also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system (See, e.g., U.S. Pat. No. 3,710,795).

#### *Intravesical Administration*

Intravesical administration, if used, is generally characterized by administration directly into the bladder and may include methods as described elsewhere herein. Other methods of intravesical administration may include those described in U.S. Patent Nos. 6,207,180 and 6,039,967, as well as other methods that are known to one of skill in the art.

### *Intrathecal Administration*

Intrathecal administration, if used, is generally characterized by administration directly into the intrathecal space (where fluid flows around the spinal cord).

One common system utilized for intrathecal administration is the APT Intrathecal treatment system available from Medtronic, Inc. APT Intrathecal uses a small pump that is surgically placed under the skin of the abdomen to deliver medication directly into the intrathecal space. The medication is delivered through a small tube called a catheter that is also surgically placed. The medication can then be administered directly to cells in the spinal cord involved in conveying sensory and motor signals associated with lower urinary tract disorders.

Another system available from Medtronic that is commonly utilized for intrathecal administration is the fully implantable, programmable SynchroMed<sup>®</sup> Infusion System. The SynchroMed<sup>®</sup> Infusion System has two parts that are both placed in the body during a surgical procedure: the catheter and the pump. The catheter is a small, soft tube. One end is connected to the catheter port of the pump, and the other end is placed in the intrathecal space. The pump is a round metal device about one inch (2.5 cm) thick, three inches (8.5 cm) in diameter, and weighs about six ounces (205 g) that stores and releases prescribed amounts of medication directly into the intrathecal space. It is made of titanium, a lightweight, medical-grade metal. The reservoir is the space inside the pump that holds the medication. The fill port is a raised center portion of the pump through which the pump is refilled. The doctor or a nurse inserts a needle through the patient's skin and through the fill port to fill the pump. Some pumps have a side catheter access port that allows the doctor to inject other medications or sterile solutions directly into the catheter, bypassing the pump.

The SynchroMed<sup>®</sup> pump automatically delivers a controlled amount of medication through the catheter to the intrathecal space around the spinal cord, where it is most effective. The exact dosage, rate and timing prescribed by the doctor are entered in the pump using a programmer, an external computer-like device that controls the pump's memory. Information about the patient's prescription is stored in the pump's memory. The doctor can easily review this information by using the programmer. The programmer communicates with the pump by radio signals that allow the doctor to tell

how the pump is operating at any given time. The doctor also can use the programmer to change your medication dosage.

Methods of intrathecal administration may include those described above available from Medtronic, as well as other methods that are known to one of skill in the art.

#### Dosage and Administration

The concentration of the active agent in any of the aforementioned dosage forms and compositions can vary a great deal, and will depend on a variety of factors, including the type of composition or dosage form, the corresponding mode of administration, the nature and activity of the specific active agent, and the intended drug release profile. Preferred dosage forms contain a unit dose of active agent, i.e., a single therapeutically effective dose. For creams, ointments, etc., a "unit dose" requires an active agent concentration that provides a unit dose in a specified quantity of the formulation to be applied. The unit dose of any particular active agent will depend, of course, on the active agent and on the mode of administration.

For the active agents of the present invention (including an  $\alpha_2\delta$  subunit calcium channel modulator or other compound that binds to the  $\alpha_2\delta$  calcium channel subunit in combination with compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors), the unit dose for oral, transmucosal, topical, transdermal, and parenteral administration will be in the range of from about 1 ng to about 10,000 mg, typically in the range of from about 100 ng to about 5,000 mg. Alternatively, for active agents of the present invention (including an  $\alpha_2\delta$  subunit calcium channel modulator or other compound that binds to the  $\alpha_2\delta$  calcium channel subunit in combination with compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors), the unit dose for oral, transmucosal, topical, transdermal, and parenteral administration will be greater than about 1 ng, about 5 ng, about 10 ng, about 20 ng, about 30 ng, about 40 ng, about 50 ng, about 100 ng, about 200 ng, about 300 ng, about 400 ng, about 500 ng, about 1  $\mu$ g, about

5  $\mu$ g, about 10  $\mu$ g, about 20  $\mu$ g, about 30  $\mu$ g, about 40  $\mu$ g, about 50  $\mu$ g, about 100  $\mu$ g, about 200  $\mu$ g, about 300  $\mu$ g, about 400  $\mu$ g, about 500  $\mu$ g, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 1,000 mg, about 1,500 mg, about 2,000 mg, about 2,500 mg, about 3,000 mg, about 3,500 mg, about 4,000 mg, about 4,500 mg, about 5,000 mg, about 5,500 mg, about 6,000 mg, about 6,500 mg, about 7,000 mg, about 7,500 mg, about 8,000 mg, about 8,500 mg, about 9,000 mg, or about 9,500 mg.

For the active agents of the present invention (including an  $\alpha_2\delta$  subunit calcium channel modulator or other compound that binds to the  $\alpha_2\delta$  calcium channel subunit in combination with compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors), the unit dose for intrathecal administration will be in the range of from about 1 fg to about 1 mg, typically in the range of from about 100 fg to about 1 ng. Alternatively, for the active agents of the present invention (including an  $\alpha_2\delta$  subunit calcium channel modulator or other compound that binds to the  $\alpha_2\delta$  calcium channel subunit in combination with compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors), the unit dose for intrathecal administration will be greater than about 1 fg, about 5 fg, about 10 fg, about 20 fg, about 30 fg, about 40 fg, about 50 fg, about 100 fg, about 200 fg, about 300 fg, about 400 fg, about 500 fg, about 1 pg, about 5 pg, about 10 pg, about 20 pg, about 30 pg, about 40 pg, about 50 pg, about 100 pg, about 200 pg, about 300 pg, about 400 pg, about 500 pg, about 1 ng, about 5 ng, about 10 ng, about 20 ng, about 30 ng, about 40 ng, about 50 ng, about 100 ng, about 200 ng, about 300 ng, about 400 ng, about 500 ng, about 1  $\mu$ g, about 5  $\mu$ g, about 10  $\mu$ g, about 20  $\mu$ g, about 30  $\mu$ g, about 40  $\mu$ g, about 50  $\mu$ g, about 100  $\mu$ g, about 200  $\mu$ g, about 300  $\mu$ g, about 400  $\mu$ g, or about 500  $\mu$ g.

A therapeutically effective amount of a particular active agent administered to a given individual will, of course, be dependent on a number of factors, including the concentration of the specific active agent, composition or dosage form, the selected mode of administration, the age and general condition of the individual being treated, the

severity of the individual's condition, and other factors known to the prescribing physician.

In a preferred embodiment, drug administration is on an as-needed basis, and does not involve chronic drug administration. With an immediate release dosage form, as-needed administration may involve drug administration immediately prior to commencement of an activity wherein suppression of the symptoms of overactive bladder would be desirable, but will generally be in the range of from about 0 minutes to about 10 hours prior to such an activity, preferably in the range of from about 0 minutes to about 5 hours prior to such an activity, most preferably in the range of from about 0 minutes to about 3 hours prior to such an activity. With a sustained release dosage form, a single dose can provide therapeutic efficacy over an extended time period in the range of from about 1 hour to about 72 hours, typically in the range of from about 8 hours to about 48 hours, depending on the formulation. That is, the release period may be varied by the selection and relative quantity of particular sustained release polymers. If necessary, however, drug administration may be carried out within the context of an ongoing dosage regimen, i.e., on a weekly basis, twice weekly, daily, etc.

#### Packaged Kits

In another embodiment, a packaged kit is provided that contains the pharmaceutical formulation to be administered, i.e., a pharmaceutical formulation containing a therapeutically effective amount of an  $\alpha_2\delta$  subunit calcium channel modulator or other compound that binds to the  $\alpha_2\delta$  calcium channel subunit in combination with one or more compounds with smooth muscle modulatory effects (including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors) for the treatment of painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients, a container, preferably sealed, for housing the formulation during storage and prior to use, and instructions for carrying out drug administration in a manner effective to treat painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. The instructions will typically be written instructions on a package insert and/or on a label. Depending on the type of formulation and the intended mode of



administration, the kit may also include a device for administering the formulation. The formulation may be any suitable formulation as described herein. For example, the formulation may be an oral dosage form containing a unit dosage of a selected active agent. The kit may contain multiple formulations of different dosages of the same agent. The kit may also contain multiple formulations of different active agents.

Many modifications and other embodiments of the inventions set forth herein will come to mind to one skilled in the art to which these inventions pertain having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the inventions are not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended embodiments. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

#### EXAMPLE 1

Evaluation of Active Agents in Treating Painful and Non-painful Lower Urinary Tract Disorders and the Related Disorders Vulvodynia and Vulvar Vestibulitis in Normal and Spinal Cord Injured Patients

Administration of the combination of an  $\alpha_2\delta$  subunit calcium channel modulator and a smooth muscle modulator on bladder capacity in an irritated bladder model is described. It is expected that these results will demonstrate the efficacy of the combination of an  $\alpha_2\delta$  subunit calcium channel modulator and a smooth muscle modulator for treatment of painful and non-painful lower urinary tract disorders and the related disorders vulvodynia and vulvar vestibulitis in normal and spinal cord injured patients as described herein.

**Methods:**

***Animal Preparation:*** Female Sprague-Dawley rats (Charles River, 250-300 g, n=15) were anesthetized with urethane (1.2 g/kg) and a jugular catheter (PE10) was inserted for access to the systemic circulation. A PE-50 catheter with a fire-flared tip was inserted into the dome of the bladder through a small cystotomy and secured by ligation for bladder filling and pressure recording. Small diameter (75  $\mu$ m) stainless steel wires were inserted percutaneously into the external urethral sphincter for electromyography. The neck was closed with suture and the abdomen covered with clear plastic cellophane in order to minimize body fluid loss. Animals were positioned on a heating pad that maintained body temperature at 37 C.

***Experimental Design:*** Following a 60-90 minute control period of normal saline infusion (0.055 ml/min) to collect baseline continuous open cystometric data, the pump was turned off, the bladder was emptied, the pump turned back on, and bladder capacity was estimated by a filling cystometrogram. Bladder infusate was then switched to 0.25% acetic acid in saline and continuous open cystometry was resumed. At 3 X 20-30 minute intervals, 1 ml/kg of saline vehicle was administered intravenously in order to ascertain vehicle effects on the acetic acid irritation of the bladder and to achieve a stable level of irritation with this dilute acetic acid solution. Following the third vehicle control, bladder capacity was again estimated as described above. Subsequently, the lowest dose of drug or combination of drug was administered intravenously, and 20 minutes later bladder capacity was again measured. This process was repeated for each drug dose until the dose-response was finished. Oxybutynin was administered at 1, 3 and 10 mg/kg and Gabapentin was administered at 30, 100 and 300 mg/kg, as the Doses 1, 2 and 3, respectively, whether each drug was given alone or as part of the combination.

***Data Analysis:*** Bladder capacity data was converted from minutes to volume, corrected to saline control values, and analyzed by non-parametric, repeated measures 1-Way ANOVA (Friedman Test) for each drug or combination, and 2-Way Analysis of Variation for comparisons between drugs and combination, from the last vehicle control through the highest drug (or combination) dose.  $P < 0.05$  was considered significant.

*Results:* Dilute Acetic Acid resulted in a ~60-70% reduction in bladder capacity that was partially reversed in a dose-dependent fashion by Oxybutynin ( $P=0.0061$ ) and Gabapentin ( $P=0.0027$ ), and completely reversed by the combination ( $P=0.0009$ ; Figure 4). 2-Way ANOVA revealed no difference between Oxybutynin and Gabapentin alone in this assay, but demonstrated that the combination was more efficacious than either alone ( $P=0.0003$  and  $0.0058$ , respectively).

*Conclusions:* While both Oxybutynin and Gabapentin are capable of partially reversing the reduction in bladder capacity induced by acetic acid irritation, the combination of the two produces a synergistic effect.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following embodiments are encompassed by the present invention:

1. A method for treating lower urinary tract disorders, which comprises administering to an individual in need thereof a therapeutically effective amount of a first component that is an  $\alpha_2\delta$  subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof.
2. The method of embodiment 1, wherein the lower urinary tract disorder is a painful lower urinary tract disorder.
3. The method of embodiment 1, wherein the lower urinary tract disorder is a non-painful lower urinary tract disorder.
4. The method of embodiment 3, wherein the non-painful lower urinary tract disorder is non-painful overactive bladder.
5. The method of embodiment 1, wherein the lower urinary tract disorder is selected from the group consisting of overactive bladder, prostatitis, prostatic dysplasia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder.
6. The method of embodiment 1, wherein the active agents are contained within a pharmaceutical formulation.
7. The method of embodiment 6, wherein the pharmaceutical formulation is a unit dosage form.
8. The method of embodiment 1, wherein the  $\alpha_2\delta$  subunit calcium channel modulator is selected from the group consisting of gabapentin, pregabalin, cis-(1S,3R)-

1-(aminomethyl)-3-methylcyclohexane)acetic acid, cis-(1R,3S)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, 1 $\alpha$ ,3 $\alpha$ ,5 $\alpha$ -(1-aminomethyl)-(3,5-dimethylcyclohexane)acetic acid, (9-(aminomethyl)bicyclo[3.3.1]non-9-yl)acetic acid, and (7-(aminomethyl)bicyclo[2.2.1]hept-7-yl)acetic acid, and derivatives and analogs thereof.

9. The method of embodiment 1, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics,  $\beta$ 3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

10. The method of embodiment 9, wherein said smooth muscle modulator is an antimuscarinic.

11. The method of embodiment 10, wherein the antimuscarinic is selected from the group consisting of:

- a. Darifenacin (Daryon<sup>®</sup>);
- b. YM-905 (solifenacin succinate);
- c. Oxybutynin (Ditropan<sup>®</sup>);
- d. S-Oxybutynin;
- e. N-desethyl-oxybutynin;
- f. tolterodine (Detrol<sup>®</sup>);
- g. Trospium (Uraplex<sup>®</sup>, Spasmex<sup>®</sup>);
- h. Propiverine (Detrunorm<sup>®</sup>);
- i. Propantheline bromide (Pro-Banthine<sup>®</sup>);
- j. Hyoscyamine sulfate (Levsin<sup>®</sup>, Cystospaz<sup>®</sup>);
- k. Dicyclomine hydrochloride (Bentyl<sup>®</sup>);
- l. Flavoxate hydrochloride (Urispas<sup>®</sup>);
- m. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
- n. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;

- o. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
- p.  $\alpha$ (+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate;
- q. 1-methyl-4-piperidyl diphenylpropoxyacetate;
- r. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
- s. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
- t. pirenzipine;
- u. methoctramine;
- v. 4-diphenylacetoxy-N-methyl piperidine methiodide;
- w. tropicamide;
- x. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and
- y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

12. The method of embodiment 9, wherein said smooth muscle modulator is a  $\beta$ 3 adrenergic agonist.

13. The method of embodiment 12, wherein the  $\beta$ 3 adrenergic agonist is selected from the group consisting of:

- a. TT-138 and phenylethanolamine compounds;
- b. FR-149174 and propanolamine derivatives;
- c. KUC-7483;
- d. 4'-hydroxynorephedrine derivatives;
- e. 2-amino-1-phenylethanol compounds;
- f. GS 332;
- g. BRL-37,344;
- h. BRL-26830A;
- i. CGP 12177;

- j. CL 316243;
- k. ICI 215,001 HCl;
- l. ZD 7114 HCl;
- m. Pindolol;
- n. (S)-(-)-Pindolol;
- o. SR 59230A HCl; and
- p. SR 58611.

14. The method of embodiment 9, wherein said smooth muscle modulator is a spasmolytic.

15. The method of embodiment 14, wherein the spasmolytic is selected from the group consisting of:

- a.  $\alpha$ - $\alpha$ -diphenylacetic acid-4-(N-methyl-piperidyl) esters;
- b. Dioxazocine derivatives;
- c. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylmorphine ethers;
- d. Quaternary salts of dibenzo[1,4]diazepinones, pyrido[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones;
- e. Endo-8,8-dialkyl-8-azobicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts;
- f. Triazinones;
- g. Piperazino-pyrimidines;
- h. Aralkylamino carboxylic acids; and
- i. Aralkylamino sulfones.

16. The method of embodiment 9, wherein said smooth muscle modulator is a neurokinin receptor antagonist.

17. The method of embodiment 16, wherein the neurokinin receptor antagonist is selected from the group consisting of: RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877 and TAK-637.
18. The method of embodiment 9, wherein said smooth muscle modulator is a bradykinin receptor antagonist.
19. The method of embodiment 18, wherein the bradykinin receptor antagonist is selected from the group consisting of: des-arg<sup>10</sup>HOE 140; des-Arg<sup>9</sup>bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; and WIN 64338.
20. The method of embodiment 9, wherein said smooth muscle modulator is a nitric oxide donor.
21. The method of embodiment 20, wherein the nitric oxide donor is selected from the group consisting of:
- a. Nitroglycerin;
  - b. Sodium nitroprusside;
  - c. FK 409 (NOR-3);
  - d. FR 144420 (NOR-4);
  - e. 3-morpholinomethylsydnorimine;
  - f. Linsidomine chlorohydrate ("SIN-1");
  - g. S-nitroso-N-acetylpenicillamine ("SNAP");
  - h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
  - i. NCX 4016 (available from NicOx S.A.);
  - j. NCX 701 (available from NicOx S.A.);
  - k. NCX 1022 (available from NicOx S.A.);
  - l. HCT 1026 (available from NicOx S.A.);
  - m. NCX 1015 (available from NicOx S.A.);
  - n. NCX 950 (available from NicOx S.A.);



- o. NCX 1000 (available from NicOx S.A.);
- p. NCX 1020 (available from NicOx S.A.);
- q. AZD 4717 (available from NicOx S.A.);
- r. NCX 1510/NCX 1512 (available from NicOx S.A.);
- s. NCX 2216 (available from NicOx S.A.);
- t. NCX 4040 (available from NicOx S.A.);
- u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
- v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
- w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
- x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
- y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
- z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;
- aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
- bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
- cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;
- dd. Nitric oxide donors as disclosed in U.S. Patent No. 5,714,511;
- ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and
- ff. Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

22. The method of embodiment 1, wherein the active agents are administered on an as-needed basis.

23. The method of embodiment 22, wherein the active agents are administered prior to commencement of an activity wherein suppression of the symptoms of overactive bladder would be desirable.

24. The method of embodiment 6, wherein the formulation is a controlled release dosage form.

25. The method of embodiment 24, wherein the formulation is a delayed release dosage form.
26. The method of embodiment 24, wherein the formulation is a sustained release dosage form.
27. The method of embodiment 25, wherein the formulation is a sustained release dosage form.
28. The method of embodiment 26, wherein the sustained release dosage form provides drug release over a time period of from about 6 hours to about 8 hours.
29. The method of embodiment 1, wherein the active agents are administered orally.
30. The method of embodiment 6, wherein the active agents are administered orally.
31. The method of embodiment 30, wherein the pharmaceutical formulation is selected from the group consisting of tablets, capsules, caplets, solutions, suspensions, syrups, granules, beads, powders and pellets.
32. The method of embodiment 32, wherein the pharmaceutical formulation comprises a tablet.
34. The method of embodiment 31, wherein the pharmaceutical formulation comprises a capsule.
35. The method of embodiment 1, wherein the active agents are administered transmucosally.

36. The method of embodiment 35, wherein the active agents are administered sublingually.

37. The method of embodiment 35, wherein the active agents are administered buccally.

38. The method of embodiment 35, wherein the active agents are administered intranasally.

39. The method of embodiment 35, wherein the active agents are administered transurethrally.

40. The method of embodiment 35, wherein the active agents are administered rectally.

41. The method of embodiment 35, wherein the active agents are administered by inhalation.

42. The method of embodiment 1, wherein the active ingredient is administered intravesically.

43. The method of embodiment 1, wherein the active agents are administered topically.

44. The method of embodiment 1, wherein the active agents are administered transdermally.

45. The method of embodiment 1, wherein the active agents are administered parenterally.

46. The method of embodiment 1, wherein the active agents are administered intrathecally.

47. The method of embodiment 6, wherein the active agents are administered intrathecally.

48. The method of embodiment 6, wherein the active agents are administered by a route of administration selected from the group consisting of: vaginally and perivaginally.

49. The method of embodiment 48, wherein the formulation is selected from the group consisting of vaginal suppositories, creams, ointments, liquid formulations, pessaries, tampons, gels, pastes, foams and sprays.

50. The method of embodiment 1, wherein the individual in need thereof is an individual suffering from a spinal cord injury.

51. The method of embodiment 50, wherein the lower urinary tract disorder is spastic bladder.

52. A pharmaceutical formulation for treating lower urinary tract disorders and adapted for transmucosal drug administration, comprising a therapeutically effective amount of a first component that is an  $\alpha_2\delta$  subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, and a carrier suitable for transmucosal drug delivery buccally, sublingually, intranasally, rectally, or by inhalation.

53. The formulation of embodiment 52, wherein the lower urinary tract disorder is a painful lower urinary tract disorder.

54. The formulation of embodiment 52, wherein the lower urinary tract disorder is a non-painful lower urinary tract disorder.

55. The formulation of embodiment 54, wherein the non-painful lower urinary tract disorder is non-painful overactive bladder.

56. The formulation of embodiment 52, wherein the lower urinary tract disorder is selected from the group consisting of overactive bladder, prostatitis, prostatic dysplasia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder.

57. The formulation of embodiment 52, comprising a solid dosage form for application to the buccal mucosa, and wherein the carrier is suitable for buccal drug delivery.

58. The formulation of embodiment 57, wherein the carrier is a hydrolyzable polymer.

59. The formulation of embodiment 57, wherein the dosage form further comprises an adhesive suitable for affixing the dosage form to the buccal mucosa.

60. The formulation of embodiment 52, comprising a dosage form for application to the sublingual mucosa, and wherein the carrier is suitable for sublingual drug delivery.

61. The formulation of embodiment 52, comprising a dosage form for application to the rectal mucosa, and wherein the carrier is suitable for rectal drug delivery.

62. The formulation of embodiment 61, comprising a rectal suppository.

63. The formulation of embodiment 52, comprising a dosage form suitable for inhalation.

64. The formulation of embodiment 63, comprising a liquid.

65. The formulation of embodiment 63, comprising a dry powder.

66. The formulation of embodiment 63, comprising an aerosol composition.

67. The formulation of embodiment 52, wherein the active agents are administered by a route of administration selected from the group consisting of: vaginally and perivaginally.

68. The formulation of embodiment 67, wherein the formulation is selected from the group consisting of vaginal suppositories, creams, ointments, liquid formulations, pessaries, tampons, gels, pastes, foams and sprays.

69. The formulation of embodiment 52, wherein the  $\alpha_2\delta$  subunit calcium channel modulator is selected from the group consisting of gabapentin, pregabalin, cis-(1S,3R)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, cis-(1R,3S)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, 1 $\alpha$ ,3 $\alpha$ ,5 $\alpha$ -(1-aminomethyl)-(3,5-dimethylcyclohexane)acetic acid, (9-(aminomethyl)bicyclo[3.3.1]non-9-yl)acetic acid, and (7-(aminomethyl)bicyclo[2.2.1]hept-7-yl)acetic acid, and derivatives and analogs thereof.

70. The formulation of embodiment 52, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

71. The formulation of embodiment 70, wherein said smooth muscle modulator is an antimuscarinic.

72. The formulation of embodiment 71, wherein the antimuscarinic is selected from the group consisting of:

- a. Darifenacin (Daryon<sup>®</sup>);
- b. YM-905 (solifenacin succinate);
- c. Oxybutynin (Ditropan<sup>®</sup>);
- d. S-Oxybutynin;
- e. N-desethyl-oxybutynin;
- f. tolterodine (Detrol<sup>®</sup>);
- g. Trospium (Uraplex<sup>®</sup>, Spasmex<sup>®</sup>);
- h. Propiverine (Detrunorm<sup>®</sup>);
- i. Propantheline bromide (Pro-Banthine<sup>®</sup>);
- j. Hyoscyamine sulfate (Levsin<sup>®</sup>, Cystospaz<sup>®</sup>);
- k. Dicyclomine hydrochloride (Bentyl<sup>®</sup>);
- l. Flavoxate hydrochloride (Urispas<sup>®</sup>);
- m. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
- n. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
- o. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
- p. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate;
- q. 1-methyl-4-piperidyl diphenylpropoxyacetate;
- r. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
- s. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
- t. pirenzepine;
- u. methoctramine;
- v. 4-diphenylacetoxy-N-methyl piperidine methiodide;

- w. tropicamide;
- x. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and
- y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

73. The formulation of embodiment 70, wherein said smooth muscle modulator is a  $\beta 3$  adrenergic agonist.

74. The formulation of embodiment 73, wherein the  $\beta 3$  adrenergic agonist is selected from the group consisting of:

- a. TT-138 and phenylethanolamine compounds;
- b. FR-149174 and propanolamine derivatives;
- c. KUC-7483;
- d. 4'-hydroxynorephedrine derivatives;
- e. 2-amino-1-phenylethanol compounds;
- f. GS 332;
- g. BRL-37,344;
- h. BRL-26830A;
- i. CGP 12177;
- j. CL 316243;
- k. ICI 215,001 HCl;
- l. ZD 7114 HCl;
- m. Pindolol;
- n. (S)-(-)-Pindolol;
- o. SR 59230A HCl; and
- p. SR 58611.

75. The formulation of embodiment 70, wherein said smooth muscle modulator is a spasmolytic.



76. The formulation of embodiment 75, wherein the spasmolytic is selected from the group consisting of:

- a.  $\alpha$ - $\alpha$ -diphenylacetic acid-4-(N-methyl-piperidyl) esters;
- b. Dioxazocine derivatives;
- c. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers;
- d. Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones;
- e. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts;
- f. Triazinones;
- g. Piperazino-pyrimidines;
- h. Aralkylamino carboxylic acids; and
- i. Aralkylamino sulfones.

77. The formulation of embodiment 70, wherein said smooth muscle modulator is a neurokinin receptor antagonist.

78. The formulation of embodiment 77, wherein the neurokinin receptor antagonist is selected from the group consisting of: RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877 and TAK-637.

79. The formulation of embodiment 70, wherein said smooth muscle modulator is a bradykinin receptor antagonist.

80. The formulation of embodiment 79, wherein the bradykinin receptor antagonist is selected from the group consisting of: des-arg<sup>10</sup>HOE 140; des-Arg<sup>9</sup>bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; and WIN 64338.

81. The formulation of embodiment 70, wherein said smooth muscle modulator is a nitric oxide donor.

82. The formulation of embodiment 81, wherein the nitric oxide donor is selected from the group consisting of:

- a. Nitroglycerin;
- b. Sodium nitroprusside;
- c. FK 409 (NOR-3);
- d. FR 144420 (NOR-4);
- e. 3-morpholinostyrene;
- f. Linsidomine hydrochloride ("SIN-1");
- g. S-nitroso-N-acetylpenicillamine ("SNAP");
- h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
- i. NCX 4016 (available from NicOx S.A.);
- j. NCX 701 (available from NicOx S.A.);
- k. NCX 1022 (available from NicOx S.A.);
- l. HCT 1026 (available from NicOx S.A.);
- m. NCX 1015 (available from NicOx S.A.);
- n. NCX 950 (available from NicOx S.A.);
- o. NCX 1000 (available from NicOx S.A.);
- p. NCX 1020 (available from NicOx S.A.);
- q. AZD 4717 (available from NicOx S.A.);
- r. NCX 1510/NCX 1512 (available from NicOx S.A.);
- s. NCX 2216 (available from NicOx S.A.);
- t. NCX 4040 (available from NicOx S.A.);
- u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
- v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
- w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
- x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
- y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
- z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;

- aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
- bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
- cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;
- dd. Nitric oxide donors as disclosed in U.S. Patent No. 5,714,511;
- ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and
- ff. Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

83. The formulation of embodiment 52, wherein the formulation is administered to an individual suffering from a spinal cord injury.

84. The formulation of embodiment 83, wherein the lower urinary tract disorder is spastic bladder.

85. A packaged kit for a patient to use in the treatment of lower urinary tract disorders, comprising: a pharmaceutical formulation comprising a therapeutically effective amount of a first component that is an  $\alpha_2\delta$  subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof; a container housing the pharmaceutical formulation during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat lower urinary tract disorders.

86. The packaged kit of embodiment 85, wherein the pharmaceutical formulation is an oral dosage form containing a unit dosage of a first component that is an  $\alpha_2\delta$  subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a unit dosage of a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, the unit dosage being a therapeutically effective dosage for treatment of lower urinary tract disorders.

86. The packaged kit of embodiment 85, wherein the lower urinary tract disorder is a painful lower urinary tract disorder.

87. The packaged kit of embodiment 85, wherein the lower urinary tract disorder is a non-painful lower urinary tract disorder.

88. The packaged kit of embodiment 87, wherein the non-painful lower urinary tract disorder is non-painful overactive bladder.

89. The packaged kit of embodiment 87, wherein the lower urinary tract disorder is selected from the group consisting of overactive bladder, prostatitis, prostatic hyperplasia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder.

90. The packaged kit of embodiment 85, wherein the  $\alpha_2\delta$  subunit calcium channel modulator is selected from the group consisting of gabapentin, pregabalin, cis-(1S,3R)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, cis-(1R,3S)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, 1 $\alpha$ ,3 $\alpha$ ,5 $\alpha$ -(1-aminomethyl)-(3,5-dimethylcyclohexane)acetic acid, (9-(aminomethyl)bicyclo[3.3.1]non-9-yl)acetic acid, and (7-(aminomethyl)bicyclo[2.2.1]hept-7-yl)acetic acid, and derivatives and analogs thereof.

91. The packaged kit of embodiment 85, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

92. The packaged kit of embodiment 91, wherein said smooth muscle modulator is an antimuscarinic.

93. The packaged kit of embodiment 92, wherein the antimuscarinic is selected from the group consisting of:

- a. Darifenacin (Daryon<sup>®</sup>);
- b. YM-905 (solifenacin succinate);
- c. Oxybutynin (Ditropan<sup>®</sup>);
- d. S-Oxybutynin;
- e. N-desethyl-oxybutynin;
- f. tolterodine (Detrol<sup>®</sup>);
- g. Trospium (Uraplex<sup>®</sup>, Spasmex<sup>®</sup>);
- h. Propiverine (Detrunorm<sup>®</sup>);
- i. Propantheline bromide (Pro-Banthine<sup>®</sup>);
- j. Hyoscyamine sulfate (Levsin<sup>®</sup>, Cystospaz<sup>®</sup>);
- k. Dicyclomine hydrochloride (Bentyl<sup>®</sup>);
- l. Flavoxate hydrochloride (Urispas<sup>®</sup>);
- m. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
- n. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
- o. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
- p. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate;
- q. 1-methyl-4-piperidyl diphenylpropoxyacetate;
- r. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
- s. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
- t. pirenzepine;
- u. methoctramine;
- v. 4-diphenylacetoxy-N-methyl piperidine methiodide;
- w. tropicamide;
- x. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and

- y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

94. The packaged kit of embodiment 91, wherein said smooth muscle modulator is a  $\beta$ 3 adrenergic agonist.

95. The packaged kit of embodiment 94, wherein the  $\beta$ 3 adrenergic agonist is selected from the group consisting of:

- a. TT-138 and phenylethanolamine compounds;
- b. FR-149174 and propanolamine derivatives;
- c. KUC-7483;
- d. 4'-hydroxynorephedrine derivatives;
- e. 2-amino-1-phenylethanol compounds;
- f. GS 332;
- g. BRL-37,344;
- h. BRL-26830A;
- i. CGP 12177;
- j. CL 316243;
- k. ICI 215,001 HCl;
- l. ZD 7114 HCl;
- m. Pindolol;
- n. (S)-(-)-Pindolol;
- o. SR 59230A HCl; and
- p. SR 58611.

96. The packaged kit of embodiment 91, wherein said smooth muscle modulator is a spasmolytic.

97. The packaged kit of embodiment 96, wherein the spasmolytic is selected from the group consisting of:

- a.  $\alpha$ - $\alpha$ -diphenylacetic acid-4-(N-methyl-piperidyl) esters;

- b. Dioxazocine derivatives;
- c. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers;
- d. Quaternary salts of dibenzo[1,4]diazepinones, pyrido[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones;
- e. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts;
- f. Triazinones;
- g. Piperazino-pyrimidines;
- h. Aralkylamino carboxylic acids; and
- i. Aralkylamino sulfones.

98. The packaged kit of embodiment 91, wherein said smooth muscle modulator is a neurokinin receptor antagonist.

99. The packaged kit of embodiment 98, wherein the neurokinin receptor antagonist is selected from the group consisting of: RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877 and TAK-637.

100. The packaged kit of embodiment 91, wherein said smooth muscle modulator is a bradykinin receptor antagonist.

101. The packaged kit of embodiment 100, wherein the bradykinin receptor antagonist is selected from the group consisting of: des-arg<sup>10</sup>HOE 140; des-Arg<sup>9</sup>bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; and WIN 64338.

102. The packaged kit of embodiment 91, wherein said smooth muscle modulator is a nitric oxide donor.

103. The packaged kit of embodiment 102, wherein the nitric oxide donor is selected from the group consisting of:

- a. Nitroglycerin;
- b. Sodium nitroprusside;
- c. FK 409 (NOR-3);
- d. FR 144420 (NOR-4);
- e. 3-morpholinosydnonimine;
- f. Linsidomine chlorohydrate ("SIN-1");
- g. S-nitroso-N-acetylpenicillamine ("SNAP");
- h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
- i. NCX 4016 (available from NicOx S.A.);
- j. NCX 701 (available from NicOx S.A.);
- k. NCX 1022 (available from NicOx S.A.);
- l. HCT 1026 (available from NicOx S.A.);
- m. NCX 1015 (available from NicOx S.A.);
- n. NCX 950 (available from NicOx S.A.);
- o. NCX 1000 (available from NicOx S.A.);
- p. NCX 1020 (available from NicOx S.A.);
- q. AZD 4717 (available from NicOx S.A.);
- r. NCX 1510/NCX 1512 (available from NicOx S.A.);
- s. NCX 2216 (available from NicOx S.A.);
- t. NCX 4040 (available from NicOx S.A.);
- u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
- v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
- w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
- x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
- y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
- z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;
- aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
- bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
- cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;



- dd. Nitric oxide donors as disclosed in U.S. Patent No. 5,714,511;
- ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and  
Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

104. The packaged kit of embodiment 85, wherein the pharmaceutical formulation is for administration to an individual suffering from a spinal cord injury.

105. The packaged kit of embodiment 104, wherein the lower urinary tract disorder is spastic bladder.

CLAIMS

What is claimed is:

1. A method for treating lower urinary tract disorders which comprises administering to an individual in need thereof a therapeutically effective amount of a first component that is an  $\alpha_2\delta$  subunit calcium channel modulator in combination with a second component that is a smooth muscle modulator, wherein:

- a. said lower urinary tract disorder is selected from the group consisting of: overactive bladder, prostatitis, prostatic hyperplasia, and spastic bladder;
- b. said  $\alpha_2\delta$  subunit calcium channel modulator is selected from the group consisting of gabapentin, pregabalin, cis-(1S,3R)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, cis-(1R,3S)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, 1 $\alpha$ ,3 $\alpha$ ,5 $\alpha$ -(1-aminomethyl)-(3,5-dimethylcyclohexane)acetic acid, (9-(aminomethyl)bicyclo[3.3.1]non-9-yl)acetic acid, and (7-(aminomethyl)bicyclo[2.2.1]hept-7-yl)acetic acid, and derivatives and analogs thereof; and
- c. said smooth muscle modulator is selected from the group consisting of: Darifenacin (Daryon<sup>®</sup>); YM-905 (solifenacin succinate); Oxybutynin (Ditropan<sup>®</sup>); S-Oxybutynin; N-desethyl-oxybutynin; tolterodine (Detrol<sup>®</sup>); Trospium (Uraplex<sup>®</sup>, Spasmex<sup>®</sup>); Propiverine (Detrunorm<sup>®</sup>); Propantheline bromide (Pro-Banthine<sup>®</sup>); Hyoscyamine sulfate (Levsin<sup>®</sup>, Cystospaz<sup>®</sup>); Dicyclomine hydrochloride (Bentyl<sup>®</sup>); Flavoxate hydrochloride (Urispas<sup>®</sup>); d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate; (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate; (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate; alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate; 1-methyl-4-piperidyl diphenylpropoxyacetate; 3'-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate; 4-amino-piperidine containing compounds as disclosed in Diouf *et al.*

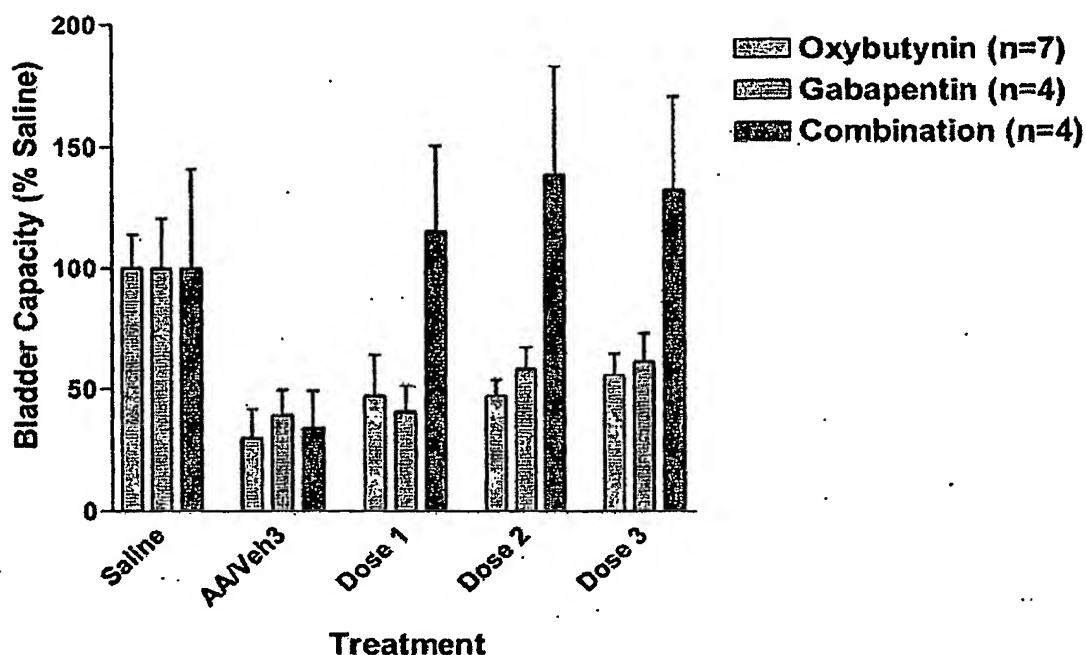
(2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;pirenzipine;  
methoctramine;4-diphenylacetoxy-N-methyl piperidine methiodide;  
tropicamide; (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-  
[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; PNU-  
200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-  
phenylpropanamine); TT-138 and phenylethanolamine compounds; FR-  
149174 and propanolamine derivatives; KUC-7483; 4'-  
hydroxynorephedrine derivatives; 2-amino-1-phenylethanol compounds;  
GS 332; BRL-37,344; BRL-26830A; CGP 12177; CL 316243; ICI  
215,001 HCl; ZD 7114 HCl; Pindolol; (S)-(-)-Pindolol; SR 59230A  
HCl; SR 58611;  $\alpha$ - $\alpha$ -diphenylacetic acid-4-(N-methyl-piperidyl) esters;  
Dioxazocine derivatives; Quaternary 6,11-dihydro-dibenzo-[b,e]-  
thiepine-11-N-alkylnorscopine ethers; Quaternary salts of  
dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones,  
pyrido[1,5]benzodiazepinones; Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1)  
octane-6,7-exo-epoxy-3-alkyl-carboxylate salts; Triazinones;  
Piperazino-pyrimidines; Aralkylamino carboxylic acids; Aralkylamino  
sulfones; RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877; L  
659,877; TAK-637; des-arg<sup>10</sup>HOE 140; des-Arg<sup>9</sup>bradykinin; NPC 349;  
NPC 567; HOE 140; MEN11270; Icatibant; FR173567; WIN 64338;  
Nitroglycerin; Sodium nitroprusside; FK 409 (NOR-3); FR 144420  
(NOR-4); 3-morpholinosydnonimine; Linsidomine chlorohydrate  
("SIN-1"); S-nitroso-N-acetylpenicillamine ("SNAP"); AZD3582; NCX  
4016; NCX 701; NCX 1022; HCT 1026; NCX 1015; NCX 950; NCX  
1000; NCX 1020; AZD 4717; NCX 1510/NCX 1512; NCX 2216; and  
NCX 4040.

METHODS FOR TREATING LOWER URINARY TRACT DISORDERS USING  $\alpha_2\delta$   
SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE  
MODULATORS

ABSTRACT OF THE DISCLOSURE

A method is provided for using  $\alpha_2\delta$  subunit calcium channel modulators or other compounds that bind to the  $\alpha_2\delta$  calcium channel subunit in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics,  $\beta_3$  adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors, to treat painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients.

**The Effect of Gabapentin (30,  
100 and 300 mg/kg),  
Oxybutynin (1, 3 and 10 mg/kg)  
and Combination on 0.25%  
Acetic Acid Induced Bladder  
Irritation**



2-Way ANOVA Analysis  
 Combo vs. Oxy,  $P=0.0003$   
 Combo vs. GP,  $P=0.0058$   
 GP vs. Oxy, NS

**Figure 1:** Graph depicting the mean  $\pm$  SEM of directly measured Bladder Capacity (as per cent of Saline Control Values) during continuous cystometry in urethane anesthetized female rats before and during bladder irritation with intravesical 0.25% acetic acid (AA) infusion, the effects of three vehicle injections ((AA/Veh 3) and the effects of cumulative, increasing intrathecal doses of oxybutynin (n=7), gabapentin (n=4), or a combination of oxybutynin and gabapentin (n=4).